The effects of resistance training and protein ingestion on skeletal muscle function in COPD

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The effects of resistance training and protein ingestion on skeletal muscle function in COPD.

By

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A thesis submitted in partial fulfilment of the University's requirements for the Degree of Doctor of Philosophy (PhD).

In collaboration with:

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Declaration

This work has been completed during the period of my registration. I declare that this thesis has been composed by myself and that the work, of which this is a record, has been performed by myself except where assistance has been acknowledged. Assistance during exercise testing and resistance training was provided by Dr Manoj Menon, Carolyn Sandland and Samantha Harrison, when required. Dr Manoj Menon acquired muscle biopsies from study participants as part of the wider Medical Research Council funded study under which, this work took place and obtained consent from some study participants.

No part of this thesis has been submitted in a previous application for a higher degree. I give permission for this thesis to be made available for consultation, photocopying and use by other libraries directly or via the British Library.

Signature:

Date: 19th December 2011

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Abstract

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a complex disease, characterised by progressive airflow obstruction and is a major cause of morbidity, mortality and healthcare usage in the UK. Quadriceps muscle dysfunction is a key cause of exercise intolerance in patients with COPD, manifested by reduced muscle mass and strength. This problem also imposes a burden to the health system as quadriceps dysfunction is an independent predictor of hospitalisation and mortality. Importantly, the quadriceps may provide a target for therapy in an otherwise irreversible lung disease and changes in strength after resistance training (RT) are well documented. Protein supplementation has been successfully used as an adjunct to RT in healthy populations. However the role of this therapeutic combination has not before been studied in a COPD population.

Methods: This thesis describes a randomised controlled trial (RCT) which aims to explore the role of protein supplementation given immediately after RT, upon functional outcomes, in patients with COPD. The hypothesis was that RT, in combination with protein ingestion (at the time of training) will have greater effects on functional outcomes than RT alone (**chapter 4**). Secondary aims were to precisely explore the training intensity progression, fatigue profile (**chapter 5**) and cardio-respiratory load imposed by the RT (**chapter 6**) and to examine the measurement properties of the ActiTrac® physical activity (PA) monitors (**chapter 7**). In all chapters the response to the intervention in patients with COPD, is compared to healthy, age-matched controls.

Results: The overriding message from this thesis is that protein supplementation can not be routinely recommended as an adjunct to RT for patients with COPD. All groups made significant improvements in quadriceps strength and thigh mass after RT but protein did not augment the outcome. Subjects with evidence of muscle wastage (based on fat-free mass criteria) responded less well to RT, although the study was underpowered to draw meaningful conclusions in this group. Subjects with COPD made comparable improvements to healthy age-matched controls, despite training at much lower intensities and experiencing greater decay in muscle force during a training session. Moreover, the RT programme was able to sufficiently activate the cardio-pulmonary system and led to significant improvements in whole-body exercise performance. PA did not change after the 8-week RT programme; suggesting that changes after RT are not routinely translated to increased habitual activity, particularly when the educational component of rehabilitation is missing.

Conclusions: The RT programme utilised in this thesis was able to significantly improve both strength and endurance-related outcomes in patients with COPD. However, the provision of additional protein at the time of training did not enhance the benefits. The isokinetic RT programme provided a unique opportunity to precisely explore the training intensity progression, fatigue profile and cardio-respiratory load imposed by the training; comparing patients with COPD and healthy controls. The findings from this work provide some important considerations for clinical practice and require further investigation within a conventional rehabilitation setting.

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Publications

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Papers

Houchen, L., Deacon, S.J., Sandland, C.J., Collier, R., Steiner, M.C., Morgan, M.D. and Singh, S.J. (2011) The preservation of lower-limb strength after a short-course of pulmonary rehabilitation with no maintenance. *Physiotherapy,* 97 (3) 264-266.

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Abstracts presented

Houchen, L., Menon, M.K., Harrison, S., Sandland, C. Morgan, M., Singh, S.J and Steiner, M.C. (2012) Training profile of an 8-week, isokinetic quadriceps resistance training programme. Comparison between patients with COPD and healthy controls. Presented at the 2012 American Thoracic Society (ATS) Conference, San Francisco and selected as a 'Best Abstract' winner for the Pulmonary Rehabilitation Group.

Houchen, L., Menon, M.K., Harrison, S., Sandland, C. Morgan, M., Singh, S.J and Steiner, M.C. (2011) Does protein supplementation enhance the effects of resistance training in patients with COPD?' Presented at the 2011 European Respiratory Society (ERS) Annual Congress, Amsterdam and selected as a 'Best Abstract' winner for the Rehabilitation Group.

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Houchen, L., Sandland C., Harrison, S., Menon, M., Steiner, M. and Singh, S. (2010) Ventilatory requirements of a quadriceps strength training programme. Thematic poster: P4045. Presented at the 2010 ERS Annual Congress, Barcelona.

Houchen,L. (2010) The role of resistance training and protein supplementation on functional outcomes in patients with COPD. Oral presentation: no.13. Presented at the 2010 Institute for Lung Health (ILH) Respiratory Science Research Meeting, National Space Centre, Leicester.

Houchen, L., Bankart, J., Singh, S.J. (2009) Pilot study to assess the discriminatory properties and reproducibility of the ActiTrac monitors. Thematic Poster: P554. Presented at the 2009 ERS Annual Congress, Vienna.

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Houchen, L., Deacon, S.J., Sandland, C.J. and Singh, S.J. (2008) The sustainability of lower-limb resistance training after pulmonary rehabilitation. A six-month follow-up study. Poster-discussion. Presented at the 2008 CSP Congress, Manchester.

Houchen, L., Deacon, S.J., Sandland, C.J., Collier, R., Vincent, E.E., Singh, S.J. and Morgan, M.D. (2007) How sustainable is lower-limb strength training after a short course of rehabilitation in COPD? A 6-month follow-up study. e-poster: E3079. Presented at the 2007 ERS Annual Congress, Stockholm.

Abbreviations
and symbols used in this Thesis

σ	sigma
°	degrees
°/sec	degrees per second
/	divided by
<	less than
≤	less than or equal to
>	more than
≥	more than or equal to
x	multiplied by
%	percent or percentage
1RM	one repetition maximum
6MWT	six minute walk test
AE	acute exacerbation
am	ante meridian "before midday"
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AOT	ambulatory oxygen therapy
ATP	adenosine tri-phosphate
ATS	American Thoracic Society

BIA	bioelectric impedance
BMD	bone mineral density
BMI	body mass index
BODE	BMI, obstruction, dyspnoea, exercise capacity
BCKQ	Bristol COPD knowledge questionnaire
BTS	British Thoracic Society
cm	centimetres
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise test
CSA	cross sectional area
CT	computed tomography
CTU	clinical trials unit
DEXA	dual energy x-ray absorptiometry
DLW	doubly labelled water
DSAI	Duke Activity Status Index
EE	energy expenditure
e.g.	for example
ERS	European Respiratory Society
ESWT	endurance shuttle walk test
et al	and others

FEV_1	forced expiratory volume in one second
FFM	fat free mass
FFMi	fat free mass index
FI	fatigue index
FVC	forced vital capacity
g	grams
GOLD	Global initiative for chronic Obstructive Lung Disease
GP	general practitioner
He	helium
HHD	hand held dynamometer or hand held dynamometry
HR	heart rate
HRQoL	health related quality of life
ICC	intraclass correlations
i.e.	id est ‘’that is’’
ILH	Institute for Lung Health
ISWT	incremental shuttle walking test

J	joules
kcal	kilocalories
kg	kilograms
kg/m^2	kilograms per metres squared
kPa	kilopascal
l	litres
LABA	long-acting beta$_2$ agonist
LAMA	long-acting muscarinic antagonist
lb	pounds
LINQ	lung information needs questionnaire
l/min	litres per minute
LTOT	long-term oxygen therapy
LVRS	lung volume reduction surgery
m	metre(s)
MCID	minimal clinical important difference
METS	metabolic equivalents
mg/kg	milligram per kilogram
mls	millilitres
mls/kg	millilitres per kilogram
MRC	Medical Research Council
MRI	magnetic resonance imaging

N	Newton
n=	number is
NETT	national emphysema treatment trial
NHS	National Health Service
NICE	National Institute for health and Clinical Excellence
NIV	non-invasive ventilation
Nm	Newton metres
NMES	neuromuscular electrical stimulation
NS	not significant
p<	probability of less than
p≤	probability of less than or equal to
PA	physical activity
PaO_2	partial pressure of oxygen in arterial blood
PAV	pre-set angular velocity
PCr	phosphocreatine
pH	the power of the hydrogen ion concentration
PhD	Doctor of Philosophy
PImax	maximal inspiratory pressure
pm	post meridian "after midday"
PR	pulmonary rehabilitation
QA	quality assurance
QOL	quality of life

r=	correlation coefficient
RCT	randomised controlled trial
RDS	research design service
REE	resting energy expenditure
RER	respiratory exchange ratio
ROI	region of interest
ROM	range of movement
RPE	rate of perceived exertion
RPM	revolutions per minute
RT	resistance training
RV	residual volume
SD	standard deviation
SE	standard error
sec	seconds
SFA	skin fold anthropometry
SGRQ	St George's respiratory questionnaire
SpO_2	saturation of peripheral oxygen
SPSS	statistical package for the social sciences
UHL	University Hospitals of Leicester NHS trust
UK	United Kingdom
US	United States
U/S	ultrasound

VE	minute ventilation
VC	vital capacity
VCO_2	carbon dioxide production
VO_2	oxygen consumption
VO_2max	maximal oxygen consumption
VO_2peak	peak oxygen uptake
W	watt(s)
W/min	watts per minute

Chapter 1

Thesis Introduction

1.1 Defining the burden of COPD

Chronic Obstructive Pulmonary Disease (COPD) is an umbrella term that describes several abnormalities of the lung often caused by tobacco smoking, including chronic bronchitis and emphysema (Anthonisen 2002) . It is a complex disease, characterised by progressive airflow obstruction, which isn't fully reversible but does not change markedly over several months (National Institute for Clinical Excellence 2010). COPD is a major cause of morbidity, mortality and healthcare usage in the United Kingdom (Britton 2003;National Institute for Clinical Excellence 2010) and therefore represents a huge burden to the individual, their family and the healthcare system. This burden is set to increase in line with tobacco usage, as COPD is projected to become the 3rd leading cause of death in the world by 2030 (World Health Organization 2008). Symptoms include dyspnoea, cough and sputum production (Anthonisen 2002). However, exercise intolerance is a key feature of advancing COPD, with patients reporting dyspnoea and leg fatigue among the most frequent symptoms which limit exercise (Killian et al. 1992) .

The clinical manifestations of COPD are not confined solely to the lungs and the systemic consequences of the disease are now well documented (Decramer et al. 2005). One extra- pulmonary feature of the disease is skeletal muscle dysfunction (American Thoracic Society/ European Respiratory Society 1999). Specifically, the loss of skeletal muscle mass and

strength (American Thoracic Society/ European Respiratory Society 1999;Gosselink et al. 1996). The mechanisms underlying skeletal muscle dysfunction in this population are not fully understood; however deconditioning through inactivity is undoubtedly involved (Decramer et al. 1994;Morgan 2005).

Whatever the cause, muscle weakness has important prognostic and functional consequences for the individual, independent of their lung function (Decramer et al. 1997a;Gosselink, Troosters, & Decramer 1996;Marquis et al. 2002;Swallow et al. 2007b) and leg fatigue negatively contributes to whole body exercise performance (Steiner et al. 2005a). These skeletal muscle alterations indicate that muscle training should play an important role in the treatment of this patient group (O'Shea et al. 2004). For many patients with COPD, the pulmonary pathology underlying their disease is irremediable. Therefore, therapies to combat the secondary consequences of the disease may be effective and warrant further investigation. With this in mind, the skeletal muscles may provide a potential target for therapy in an otherwise irreversible lung disease and this is a key aim of Pulmonary Rehabilitation (PR).

We know that resistance training (RT) in isolation can improve muscle mass and strength in patients with COPD (O'Shea, Taylor, & Paratz 2004;Spruit et al. 2002). Increases in quadriceps strength are well documented (O'Shea et al. 2009a) and improvements after training are generally in the region of 20% (Bernard et al. 1999;Spruit et al. 2002). Mass is less commonly measured in

this population. Furthermore changes in mass after exercise tend to be much lower than changes in strength (only 5-6% improvements); suggesting that other factors (besides increased mass) are involved in producing muscle force (Jones et al. 2004). Whether these improvements in muscle strength and mass translate into functional benefits for patients is inconclusive (O'Shea, Taylor, & Paratz 2009).

RT has generally been prescribed quite crudely for practical purposes within rehabilitation settings, using equipment which is locally available and transportable. Isokinetic dynamometry represents the gold standard in the observation of muscle performance for testing and training. The presence of an accommodating resistance during isokinetic testing allows for the safe measuring of torque, total work and power at constant speed throughout the full range of movement and therefore gives a comprehensive picture of muscle function. Isokinetic testing is rarely used in the evaluation of strength for patients with COPD and has not been used as a RT device in this population. The unique RT programme used in this thesis was based upon some novel research by Jones conducted at the University of Nottingham in 2004. They found that by immobilising healthy young men in a limb cast for 2 weeks, a 5% decrease in quadriceps mass occurred. Following a carefully controlled isokinetic RT programme at 180 degrees per second (°/ sec); muscle mass and strength returned to basal levels. The rapid training velocity chosen targets type II muscle fibres and was found to be feasible and acceptable to our frail patients in a pilot study which took place prior to commencing this thesis (Williams et al. 2007).

Skeletal muscle mass is determined by varying rates of protein synthesis and protein degradation. Therefore muscle atrophy may be expressed in terms of decreased protein synthesis and/ or increased protein degradation resulting in net protein loss. Evidence suggests that there is increased whole body protein turnover in underweight patients with COPD (Engelen 2000), although the mechanisms are poorly understood. Dietary protein has been shown to induce protein synthesis in healthy young adults. However there is an impaired response in healthy elderly subjects and merely providing dietary protein may not be effective in increasing protein synthesis (Cuthbertson et al. 2006). It may be that an anabolic stimulus, such as exercise is needed. The timing of supplementation in relation to resistance exercise may also be an important factor in the response for older people. Data from Denmark found that muscle hypertrophy only occurred in the group receiving protein immediately after resistance training and not in those receiving the protein 2 hours later (Esmarck et al. 2001). The aim of this thesis was to translate these observations to a group with COPD as the role of protein in combination with RT has not before been studied in this population.

1.2 Research Aim and Research Objectives

This thesis aims to address gaps in the existing field of knowledge. We currently do not know what the effects of this therapeutic combination (RT and protein supplementation) will be. Furthermore we do not know if the results will translate into functional benefits for patients. This was a mechanistic study, examining the role of protein as an adjunct to RT. It was not a study of dietary protein for patients, in isolation, or alongside generic rehabilitation. The

study hypothesis was that: RT, in combination with protein (at the time of training), will have greater effects on functional outcomes than RT alone.

Furthermore, the nature of the RT programme chosen presented unique opportunities to precisely explore the training intensity progression, fatigue profile and cardio-respiratory load imposed by the training; comparing patients with COPD and healthy controls.

Specific objectives were to measure the functional response to the intervention by observing changes in muscle function (muscle strength and mass) and physical performance [whole-body exercise capacity and physical activity (PA)]. The effects in patients with COPD are compared with healthy, age-matched controls.

The following research objectives were formulated:

1. To observe the changes in muscle function and physical performance after a RT programme.

2. To then determine whether the addition of a nutritional supplement has increased benefits on muscle function and physical performance in patients with COPD; compared to RT alone.

3. To describe the trajectory of training intensity progression and fatigue profile of the isokinetic RT programme over an 8-week period and to observe how training intensity relates to changes in outcome measures.

4. To analyse the cardio-respiratory load imposed by the RT programme.

5. To explore the test re-test reliability, reproducibility and sensitivity of the ActiTrac® accelerometers, used to assess PA in this thesis.

1.3 Structure and Setting of the Thesis

This thesis forms part of a larger Medical Research Council (MRC) funded study which was designed to explore the molecular mechanisms underpinning the restorative effects of RT and protein supplementation on muscle mass in patients with COPD (*'Molecular approaches to reversing skeletal muscle wasting in COPD. The role of resistance training and nutritional supplementation*'). Dr Manoj Menon obtained vastus lateralis muscle biopsies to examine the molecular responses to the intervention for his PhD thesis. My thesis focuses on the functional outcomes from the randomised controlled trial (RCT) of RT and nutritional supplementation, in patients with COPD. The RCT is described in **chapter 3** (materials and methods). Both myself and Dr Menon recruited and consented patients, performed cycle ergometry tests and carried out DEXA (dual energy x-ray absorptiometry) scans. I, independently, supervised RT and assessed muscle strength. My thesis was therefore limited, in part, due to the design of the study which was beyond my control (e.g. timings, duration of programme, interventions delivered).

Chapter 2 presents a comprehensive review of the available literature and contextualises this thesis. **Chapter 4** presents the main outcomes from the RCT and explores the role of RT (± protein supplementation) upon muscle

function and physical performance after the 8-week intervention. As protein supplementation did not augment the benefits of RT, after this chapter, the data from the subgroups are pooled.

Chapters 5 and 6 explore the profile of the RT programme; comparing training trajectories, fatigue/ force decay and the cardio-respiratory load in patients with COPD and healthy controls. The relationship between training intensity and functional outcomes at 4 and 8-weeks is also analysed.

Chapter 7 is a methodological chapter relating to PA. The reliability properties of the ActiTrac® activity monitors, used to measure PA in this thesis, are interrogated. The changes in PA (measured using the ActiTrac® and questionnaires), following RT in a sub-group of patients are also presented.

Finally **chapter 8** discusses the key findings, implications for clinical practice, and ideas for future work which have arisen from the conduct of this thesis.

Chapter 2

Literature Review

2.1 Introduction

This chapter helps to contextualise the thesis by exploring the main themes. Firstly the disease pathology, epidemiology and clinical features of Chronic Obstructive Pulmonary Disease are introduced. A major cause of exercise limitation in this population is skeletal muscle dysfunction. The possible causes and consequences of this problem are discussed. Current treatments used to slow disease progression, improve symptoms, exercise tolerance and quality of life are appraised. Finally the chapter concludes by outlining the two interventions explored (resistance training and protein supplementation) and the outcome measures used in this thesis.

2.2 Chronic Obstructive Pulmonary Disease

2.2.1 Definition

Chronic obstructive pulmonary disease (COPD) is an umbrella term that describes several abnormalities of the lung including chronic bronchitis and emphysema (Anthonisen 2002). COPD is a preventable and treatable disease characterised by progressive airflow obstruction. This obstruction is not fully reversible but does not change markedly over several months (Department of Health 2010;National Institute for Clinical Excellence 2010).

COPD is diagnosed by an objective measure of airflow obstruction; spirometry. Airflow obstruction is defined as a reduced FEV_1/FVC ratio (where

FEV_1 is forced expired volume in one second and FVC is forced vital capacity). An FEV_1/FVC ratio of less than 0.7 (70%) indicates COPD (National Institute for Clinical Excellence 2010). The FEV_1 is also commonly reported as an independent measure of airflow obstruction which can be expressed as a percentage of the value predicted for that individual [based on age, height and gender (Department of Health 2010;Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2009)]. GOLD classify disease severity in four stages based on FEV_1 and FEV_1/FVC ratio criteria, these stages are heavily cited [table 2.1 (Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2009)].

Table 2.1 GOLD classification of COPD severity by spirometry

Classification	**Spirometry values**
I: Mild	• FEV_1/FVC <70% • FEV_1 ≥ 80% predicted
II: Moderate	• FEV_1/FVC <70% • FEV_1 ≥ 50 and < 80% predicted
III: Severe	• FEV_1/FVC <70% • FEV_1 ≥ 30 and < 50% predicted
IV: Very Severe	• FEV_1/FVC <70% • FEV_1 < 30% predicted OR < 50% predicted plus respiratory failure

2.2.2 Pathology and clinical features

In the past, distinctions were made between the individual diseases which are now incorporated by the term COPD. This section discusses those individual diseases in more detail. However, for practical purposes, these conditions have been grouped together because they usually co-exist within the same

individual and the management is much the same (Department of Health 2010).

Chronic Bronchitis

Chronic bronchitis is defined as the presence of a cough, which is productive of sputum, occurring on most days for at least 3-months of at least two successive years. The disease is characterised by inflammation of the large airways, mucous gland hypertrophy and hyperplasia, resulting in an over production of mucous (Kon & Brame 2008). This provides the ideal environment for infections to thrive. The combination of inflammation and sputum plugging causes airway narrowing.

Emphysema

Emphysema is described when the alveolar walls are destroyed, resulting in permanent dilatation of the airways, distal to the bronchioli, without obvious fibrosis. It is thought that this destruction occurs because of inflammation within the lung parenchyma (Kon & Brame 2008).

Patients with emphysema also have increased lung volumes because of air trapping which occurs as a result of expiratory flow limitation (Man and Kon 2008). This ‘air trapping’ is known as hyperinflation which is apparent on both physical examination and imaging, and is particularly evident during exercise [dynamic hyperinflation (Ries et al. 2007)].

Clinical features of COPD

The symptoms of COPD include dyspnoea, cough and sputum production (Anthonisen 2002), which may be worse during winter months (Department of Health 2010). Initially, dyspnoea does not inhibit daily tasks and these symptoms are often not present until the disease is relatively well advanced. The severity of breathlessness can be classified using the modified Medical Research Council (MRC) grade [table 2.2- (Flectcher et al. 1959)].

Table 2.2 Modified Medical Research Council dyspnoea grades

Grade	Level of breathlessness
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100m or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

COPD is a systemic disease which affects organs outside of the lungs (Decramer et al. 2005). A key problem is skeletal muscle dysfunction (weakness and atrophy), leading to exercise intolerance (Killian et al. 1992). The resultant inactivity from avoiding uncomfortable symptoms leads to worsening exercise tolerance and progressive disability (American Thoracic Society/ European Respiratory Society 1999;Rochester 2003). These changes are associated with a reduced quality of life and are often described as a ‘vicious cycle’ of physical and psychosocial decline (Agusti 2005). Patients with COPD are also at an increased risk of cardiovascular disease

which has been linked to increased arterial stiffness (Sabit et al. 2007). The arterial stiffness found in this population is greater in those with evidence of osteoporosis and is associated with inflammation (Sabit et al. 2007).

COPD is also characterised by acute exacerbations (AE) or 'flare ups.' This describes periods of the illness where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations (National Institute for Clinical Excellence 2010;Rodriguez-Roisin 2000). During an AE, dyspnoea is generally worse and sputum expectoration may change (more than usual, more viscous or more purulent). These symptoms often necessitate a change in treatment [e.g. antibiotics and/or oral steroids required (Rodriguez-Roisin 2000)]. Disease exacerbations are associated with worsening quality of life (Seemungal et al. 1998), speedier disease progression (Donaldson et al. 2002), increased mortality (Soler-Cataluna et al. 2005) and are a significant cause of hospitalisations and health care costs (Garcia-Aymerich et al. 2003). On average, 15% of those admitted to hospital die within three months, and around 25% die within a year of admission. Recent data published by the office for UK National Statistics show that one in three people with COPD are being readmitted within 28 days of discharge (British Lung Foundation and British Thoracic Society 2010).

2.2.3. Aetiology and natural history

Tobacco smoking is the single most important and preventable cause of COPD development (Department of Health 2010;van Durme et al. 2009), which generally occurs after a smoking history of twenty pack years or more

[one pack year= 20 cigarettes smoked per day for one year (Bloch and Kon 2008)]. Over time, cigarette smoking causes cycles of inflammation and repair. These cycles are associated with protein degradation, airway and parenchymal remodelling. However, non-smokers can also develop COPD due to other causes. These include exposure to pollution, occupational dusts/ fumes/ solvents and previous respiratory infections. The disease is also more prevalent in those with a poor diet and low socio-economic status (Department of Health 2010;Hansel and Kon 2008). Some individuals may additionally have a genetic deficiency of alpha-$_1$-antitrypsin. This is an anti-protease which opposes the protease elastase. Without opposition, elastase attacks the alveolar sacs of the lungs (Stoller and Aboussouan 2005).

Measuring the annual rate of loss of FEV_1 is the classic way of recording the natural history of COPD. The decline in FEV_1 can be slowed by smoking cessation (Scanlon et al. 2000). In addition to lung function, it is also important to measure the systemic effects of the disease. The BODE index is a useful prognostic indicator and incorporates body mass (B), airflow obstruction (O), dyspnoea score (D) and exercise performance [E (Celli et al. 2004)].

2.2.4. Prevalence, burden of disease and mortality

An estimated 210 million people have COPD worldwide (World Health Organization 2009). This burden is set to increase in line with tobacco usage, as COPD is projected to become the third leading cause of death in the world by 2030 (World Health Organization 2008). In the UK, around 900,000 people have a diagnosis of COPD and a further two million are estimated to have the

disease but this is yet to be diagnosed (Healthcare Commission 2006). These people are referred to as ‘the missing millions’ in the COPD strategy consultation document, launched in February 2010 (Department of Health 2010). Recent data from Canada suggests that one in four people are likely to be diagnosed and receive medical attention for COPD during their lifetime (Gershon et al. 2011).

Whilst other major causes of death have been declining, mortality due to COPD continues to rise. One person every 20 minutes dies from COPD in England and Wales, attributing to 25,000 deaths per year (UK National Statistics 2008). Mortality data may underestimate the impact of COPD as it is often listed as a contributory cause of death or not listed at all on death certification (Pauwels et al. 2001b).

COPD is a major cause of morbidity, mortality and healthcare usage in the United Kingdom (Britton 2003;National Institute for Clinical Excellence 2010) and therefore represents a huge burden to the individual, their family and the healthcare system in terms of long-term management and disability-related costs The direct cost of COPD to the UK health system is estimated to be between £810 and £930 million per year (Department of Health 2010).

2.3 Skeletal muscle dysfunction

Prior to considering the problem of skeletal muscle dysfunction in patients with COPD, it is useful to review healthy muscle structure, physiology and energy metabolism.

2.3.1 Healthy muscle structure, function and response to training

Muscle structure

Skeletal muscle tissue makes up over one-third of total body mass (Palastanga et al. 2006). Skeletal muscle consists of several individual cells which are long multinucleated fibres. Muscle fibres can shorten to around half of their original resting length, therefore the arrangement of fibres within a muscle determines how much the muscle will shorten during a contraction (Palastanga, Field, & Soames 2006). The arrangement of fibres within a muscle will either be parallel (fusiform) or oblique (pennate) to the line of pull for the whole muscle (Palastanga, Field, & Soames 2006). Muscles are attached to bones and other structures via dense connective tissue, namely tendons. When a muscle or tendon passes over a bone it is usually separated from the bone surface by bursae (fluid filled sacs); which help to reduce friction (Palastanga, Field, & Soames 2006).

Muscle fibres which are collectively supplied by one motor endplate (neurone) make up a ‘motor unit’. The motor unit comprises the alpha motor neurone and all of the muscle fibres which this innervates. The electrical impulse from this nerve ending is transmitted along the fibre by the sarcolemma, a thin membrane encasing the muscle fibre. This membrane also conducts fuels and waste products in and out of the muscle cell from the surrounding capillaries (Sherwood 1993). Each muscle cell contains specialised contractile elements; known as myofibrils.

Amino acids are the building blocks of proteins and skeletal muscle is the body's main protein store. In extreme conditions, such as starvation, muscle can supply amino acids to other tissues (Jagoe and Engelen 2003).

Muscle contraction mechanism and contraction types

Each myofibril is made up of a uniform arrangement of thick (myosin) and thin (actin) protein filaments. Excitation of the skeletal muscle fibre by its motor neurone brings about a contraction by a series of events that result in the thin filaments sliding closer together between the thick filaments. This 'sliding-filament' mechanism of muscle contraction is switched on by calcium release which binds to the protein complex troponin on the actin filaments and uncovers actin's cross bridge binding sites. After the exposed actin binds to the myosin cross bridge; energy is released which powers the rowing action of the thick and thin filaments as they slide past each other. Inward sliding of all the thin filaments causes the whole muscle to shorter (Sherwood 1993). This cycle continues as long as calcium is still present and energy is available [from the breakdown of adenosine tri-phosphate (ATP)].

Muscle contractions may occur both when the muscle is at a static length and when the length changes (shortens or lengthens under tension). See table 2.3. The two outcomes of interest in isokinetic contractions are peak torque and total work. These are described in more detail in section 2.6.1 (*quadriceps muscle strength*).

Table 2.3 Types of muscle contractions

Name	Definition
Static/ Isometric	The length of the muscle fibres remain constant during the contraction and no movement occurs at the joint.
Dynamic	Joint movement occurs during contraction. This can consist of either isotonic or isokinetic contractions.
Isotonic	There is a shortening (concentric action) and lengthening (eccentric action) of a muscle throughout its range of motion around a joint.
Isokinetic	The speed of muscle contraction is fixed within a range of motion, and the force generated by the muscle encounters an opposing force relative to that applied to the testing device.

Quadriceps Femoris muscle group

The muscles of interest in this thesis are the quadriceps (femoris); a group of four muscles which contract to extend the knee joint (rectus femoris, vastus lateralis, vastus medialis and vastus intermedius). The rectus femoris also plays a role in hip flexion, as its tendon originates above the hip joint. The other three muscles originate along the shaft of the femur (thigh) and all four join together around the patella to form the ligamentum patellae, which inserts into the tibial tuberosity (figure 2.1). Each muscle within the quadriceps 'comes into play' during different ranges of movement (Palastanga, Field, & Soames 2006).

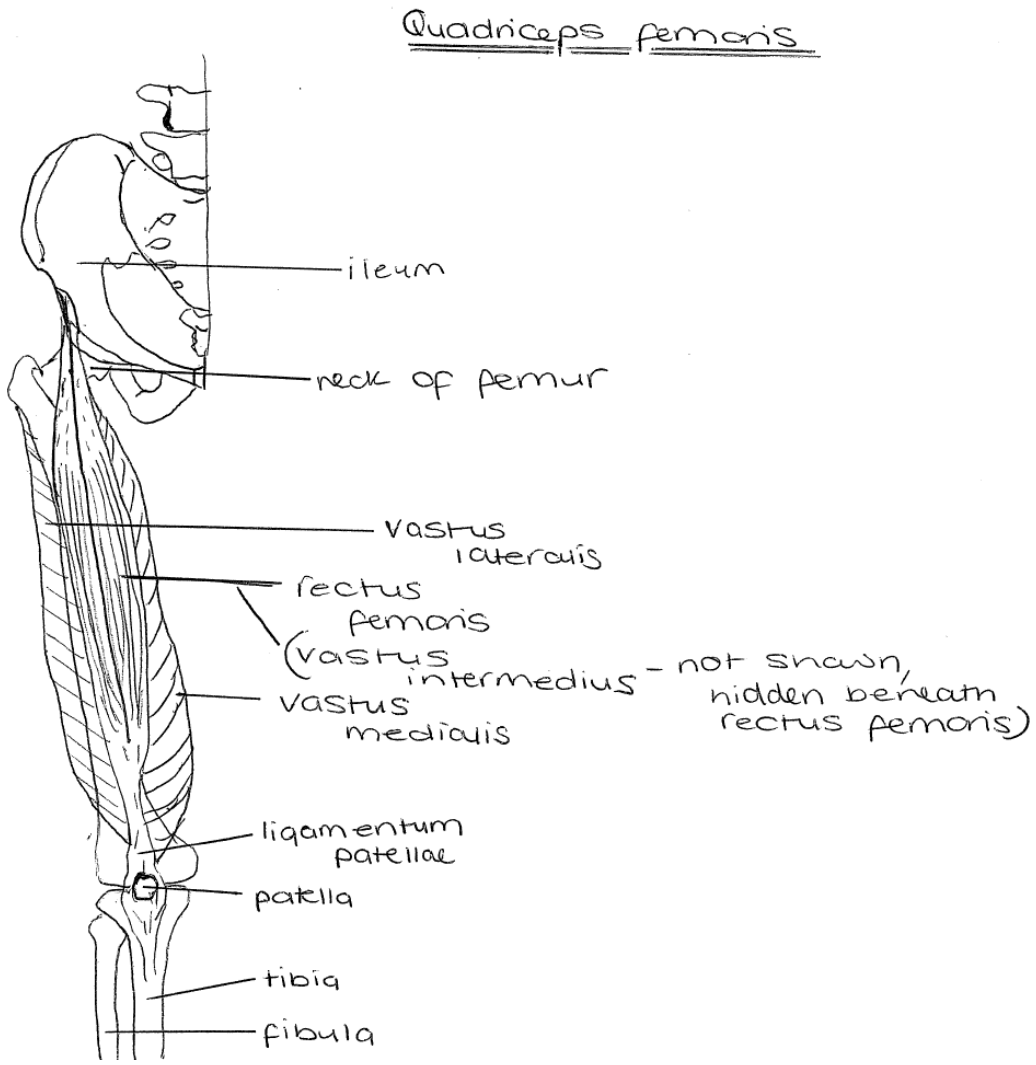


Figure 2.1 Line drawing of the Quadriceps femoris group of muscles

Two of the four muscles, rectus femoris and vastus intermedius, give central power to knee extension, working through the patella as a lever. Vastus lateralis and vastus medialis assist in knee extension but also give peripheral support to both movement and the joint itself (Backhouse 2012).The quadriceps is of particular importance because it is heavily utilised in daily function (e.g. standing from a chair, climbing stairs) and is known to be more affected by the systemic consequences of COPD, compared to other muscles (Bernard et al. 1998;Man et al. 2003a). The quadriceps muscles lose strength

and mass rapidly (within days) if disused or injured (Di Monaco et al. 2007;Ferrando et al. 1996a;Rittweger et al. 2005;Visser et al. 2000)Normal values for quadriceps strength have been reported for young and middle aged adults (American College of Sports Medicine 2009). However data from older individuals is sparse.

Table 2.4 summarises normal values for both isometric and isokinetic quadriceps strength in two studies which have evaluated these measures in a range of age groups (Borges 1989;Phillips et al. 2000a). These values are interesting when comparing values in patients with COPD to healthy controls of various ages. It should be noted, however, that variations exist between the knee joint angles and speeds for testing in this thesis and these studies. This should be taken into account when considering the results from this thesis in comparison to these studies.

Energy metabolism

ATP is required during the following three steps of contraction-relaxation:

1. To provide the energy for the power stroke of the cross bridge.
2. Permits detachment of the myosin bridge from the actin filament so that the cycle can be repeated.
3. The transport of calcium at the end of the contraction depends on the energy derived from the breakdown of ATP (Sherwood 1993).

Table 2.4 Normal values for isometric and isokinetic quadriceps strength in healthy adults aged 20-70 years.

Author (year)	Equipment used	Subjects	Isometric testing procedure	Isokinetic testing procedure
Borges (1989)	Cybex	n= 139 males and 141 females. Representing those in decades 20-70 years. Moderate activity/ inactive.	Right and left knee extensors (right leg reported). Knee fixed at 90° flexion. **Male range: 187 (38) Nm in 70 year olds to 301 (56) Nm in 20 year olds.** **Female range: 116 (23) Nm in 70 year olds to 169 (34) Nm in 20 year olds.**	Right and left knee extensors (right leg reported). ROM: 0-90°. 2 speeds: 90 and 150°/sec. **Male range (60°/sec): 143 (24) Nm in 70 year olds to 231(32) Nm in 20 year olds.** **Female range (60°/sec): 98 (17) Nm in 70 year olds to 143 (25) Nm in 20 year olds.** **Male range (150°/sec): 113 (22) Nm in 70 year olds to 180 (24) Nm in 20 year olds.** **Female range (150°/sec): 74 (12) Nm in 70 year olds to 110 (18) Nm in 20 year olds.**
Phillips (2000)	Kin-Com	n=200. 20 male and 20 female from each decade. Range 20-69 years.	Dominant knee extensors. Knee fixed at 60° flexion. **Male range: 176 (30) Nm in 60-69 year olds to 230 (51) Nm in 20-29 year olds.** **Female range: 97 (29) Nm in 60-69 year olds to 146 (33) Nm in 20-29 year olds.**	Dominant knee extensors. ROM: 0-90°. 2 speeds: 60 and 120°/sec. **Male range (60°/sec): 105 (19) Nm in 60-69 year olds to 146 (30) Nm in 20-29 year olds.** **Female range (60°/sec): 66 (15) Nm in 60-69 year olds to 97 (19) Nm in 20-29 year olds.** **Male range (120°/sec): 93 (17) Nm in 60-69 year olds to 131 (26) Nm in 20-29 year olds.** **Female range (120°/sec): 59 (13) Nm in 60-69 year olds to 85 (18) Nm in 20-29 year olds.**

Results are mean torque (SD). °, degrees; °/sec, degrees per second; Nm, Newton-metres; ROM, range of movement.

ATP is the single energy source that can be used for these processes and must be continuously supplied for activity to continue. There are three types of muscle fibres present in skeletal muscle which are classified by which of the three pathways they use for ATP synthesis. The characteristics of these fibre types are summarised in table 2.5.

Table 2.5 Characteristics of skeletal muscle fibre types

	Type I Slow-Oxidative	Type IIa Fast-Oxidative	Type IIb Fast-Glycolytic
Speed of contraction	Slow	Fast	Fast
Endurance/Fatigue Resistance	High	Medium	Low
Power of contraction	Low	High	High
Metabolism	Oxidative	Oxidative, glycolytic	Glycolytic
Mitochondrial Density	High	Medium	Low
Capillary Density	High	Medium	Low
Colour of fibre	Red	Red	White

Adapted from (Maughan et al. 1997;Sherwood 1993).

Metabolites, such as lactate (lactic acid) and ammonia are the end products of anaerobic glycolysis and are associated with fatigue (Tesch et al. 1978).

Determining muscle strength

Muscular strength is defined as 'the amount of force an individual can produce during a single maximum effort'. The term power is often used interchangeably but actually refers to the rate of force production (Costill et al. 1992). The force generated by skeletal muscle depends on: the number of

motor units recruited, fibre cross-sectional area (CSA) and two important relationships, which are:

1. The length-tension relationship: tension or force produced by a muscle is dependent upon the length of the muscle and each muscle has an optimal length for maximal force generation (Rack and Westbury 1969). This represents a function of the amount of overlap between actin and myosin filaments. If a muscle length changes, shorter or longer, force is reduced (Gaines and Talbot 1999).

2. The force-velocity relationship: The power of a contraction is dependant on the velocity at which the muscle fibres shorten and the load to be moved. Power is equal to load multiplied by velocity. With a large load, the speed of fibre shortening is slow (Gaines & Talbot 1999). Also torque exerted during isokinetic testing decreases with increasing pre-set angular velocity (PAV). Therefore more force is generated at a speed of 60 °/sec compared to 180 °/sec (Baltzopoulos and Brodie 1989).

Muscle quality also plays a role in force development as well as the factors outlined above. Quality relates to force produced per muscle area and can be related to fibre type, fatigability, blood supply to the muscle, neural activity and ability to produce/ efficiency of use of muscle energy substrates. Neural drive is particularly important in strength development and relates to motor unit recruitment, motor unit firing rate and synchronisation of motor unit firing. Importantly, these factors can be improved with RT, in the absence of muscle

hypertrophy and should therefore be considered when measuring strength (Broughton 2001).

Motivation will also have an influence on muscle strength and is discussed further in section 2.5.1 (*resistance training*).

Fatigue

Muscle fatigue is an important area of research as it is essential for daily living tasks, sporting activities and has been implicated as a possible cause of musculo-skeletal injuries (Corin et al. 2005). However it is a challenging area as the term 'fatigue' has been poorly defined in the literature and is used to describe a variety of processes related to muscle strength (Crowther et al. 2007). In simple terms, it is 'an exercise-induced reduction in maximal voluntary muscle force which is reversed by rest' (Gandevia 2001). Other authors describe fatigue in terms of 'task failure' (Maluf and Enoka 2005). Exercise or task-induced fatigue can be described as: muscular (accumulation of metabolites and depletion of energy reserves), neuromuscular (unable to sustain neural stimuli, i.e. reduced neural motor drive) or central [psychological due to motivation (Sherwood 1993)] and will depend upon the demands of the exercise or task [i.e. intensity, muscle groups involved (Maluf & Enoka 2005)].

The optimal measurement of fatigue has not been established. Therefore the tools to measure muscle fatigue have often not been assessed or validated (Corin, Strutton, & McGregor 2005). Fatigue can be induced isometrically or

isokinetically (Corin, Strutton, & McGregor 2005) and is frequently measured after a fatiguing task by recording force/ torque decay, by assessing changes in electromyography (EMG) signals or a combination of the two (Abdalla et al. 2007). The fatigue index (FI) was originally proposed by Thorstensson and Karlsson in 1976. This calculates the amount of muscle fatigue using the following equation:

FI= final force/ initial force x 100

(Thorstensson & Karlsson 1976).

It is therefore a ratio measure or percentage and may be more appropriately described as force decay. In this approach, the decline in torque output of the quadriceps after 50 contractions was expressed as a percentage of the highest of the first three torques to the last three torques. A high fatigue index indicates high fatigue resistance (FR), i.e. an increased ability to sustain muscular contraction. If the value is greater than or equal to100%, no fatigue has occurred. Variations on this FI have also been reported e.g. initial force – final force/ initial force x 100. Using this equation, a lower score indicates better FR. Authors since have adapted the index to look at the difference between the first and last third of the test or the first and last five repetitions, for instance (Davies et al. 2000). An endurance protocol may also look to test individuals until they produce a pre-defined reduced in peak torque, 50% seems to be the norm (Burdett & Vanswearingen 1987;Schwendner et al. 1995).

Corin and co-workers have found that isometric testing is better (the most valid) at evoking fatigue in the trunk flexors and extensors than isokinetic testing (Corin, Strutton, & McGregor 2005). Using four different protocols, the authors were observing for the greatest reduction in maximal muscle force in 16 university rugby players. The 'best' protocol (at evoking fatigue) reduced flexor peak torque by an average of 16.2% and extensor peak torque by 8.8%, compared to before fatigue testing using the FI described above (Thorstensson & Karlsson 1976).

Fatigue may also be expressed as time until exhaustion/ task failure using repeated contractions (Maluf & Enoka 2005;Patton et al. 1978). However, this methodology can be time consuming and impractical. Several authors propose the use of RT to fatigue or failure to enhance strength gains. There is an argument that fatigue may, in itself, provide the stimulus to improve strength by activating muscle repair processes in response to mechanical stress (Izquierdo et al. 2006;Rooney et al. 1994). Abdalla and colleagues found that there was a rise in back extensor torque following a one minute maximal fatigue protocol (Abdalla, McGregor, & Strutton 2007). They argued that this could be attributed to post-activation potentiation (prior muscle loading induces central nervous system stimulation).

Fatigue resistance (FR) is another frequently occurring term in the literature and is defined as 'the capacity to resist fatigue in conditions of prolonged strength use' (Salvador et al. 2009). FR is required during exercise and many activities of daily living, and is associated with blood lactate concentrations

(Dipla et al. 2009). Generally, fatigue and FR are measured during strength testing (during one session). However it may be important to look at these factors serially, during a RT programme. One study by Salvador and colleagues analysed FR in young healthy subjects (mean age 21 years) over an 8-week RT programme (Salvador et al. 2009). The RT included 3 sets of 8-12 repetitions for bench press, squat and arm curl. Strength and FR improved in both males and females after training ($p<0.05$ compared to baseline). The increases in strength were accompanied by a mean percentage change in FI of - 17.3% in males and - 31.3% in females; when the three RT exercises were combined. This study used the alternative FI were a lower score indicates greater FR. Other studies have supported this notion that RT can improve FR (Campos et al. 2002;Izquierdo et al. 2006;Kemmler et al. 2004) and that women are more fatigue resistant than men at baseline and after training (Clark et al. 2005;Pincivero et al. 2003). The fact that men exhibit a higher tendency for muscle fatigue may be related to their ability to produce greater peak muscle force initially (Pincivero, Gandaio, & Ito 2003), as the FI is a ratio based on the initial force generated.

The majority of studies exploring fatigue, derived from isokinetic methods, have focused on peak torque (maximal strength) as an outcome, rather than total work (cumulative). Therefore the fatigue characteristics of isokinetic work remain largely unknown in healthy and diseased populations.

Response to RT

Long-term adaptive changes occur in skeletal muscles, depending on the demands placed on the muscle. These demands must be greater than habitual levels of activity (principle of overload).

Anaerobic RT increases the diameter of glycolytic (type II) fibres and the number of muscle cells [hyperplasia (Sherwood 1993)]. Hypertrophy following RT requires net protein synthesis within the muscle fibres and that the exercise stimulus be sufficiently intense (Esmarck et al. 2001). The transient increase in protein synthesis after an acute bout of RT persists for up to 48 hours after training (Phillips et al. 1997). Protein synthesis rates are greater at three hours post-exercise, when compared to 24 and 48-hours (Phillips et al. 1997). Muscle glycogen and phosphocreatine stores are also increased with RT. In addition, each muscle fibre is linked with a population of satellite cells. These cells are capable of dividing and fusing with existing fibres. This fusion appears to be an essential part of fibre hypertrophy and therefore muscle growth. The type and magnitude of these changes will depend upon the frequency, intensity and duration of training and will only take place in the mode of performance by which the training occurs [principle of specificity (Maughan, Gleeson, & Greenhaff 1997)].

Outside of the individual fibres; neural adaptation after RT has been inferred because several studies report increases in muscle strength with little or no change in cross sectional area of the muscle (Bandy et al. 1990). This highlights that other factors (besides increased mass) are involved in

producing muscle force (Jones et al. 2004). Neural adaptations describe the development of more efficient neural pathways along the route to the muscle to improve contraction quality. The increases in muscle strength during the initial periods of a RT programme are more associated with these neural adaptations (Moritani & deVries 1979), rather than changes in fibre size which occur later (Sale 1988).

Isokinetic training will increase maximum torque at the training velocity. It has been noted by several authors that peak torque also improves at velocities above and below the training velocity. Several studies have shown that training at peak angular velocity (PAV's) of 60, 120, 180 and 240°/sec produce equitable improvements in isokinetic peak torque. The carry over may be as great as 210°/sec below and up to 180°/sec above the training velocity (Kraemer et al. 2000). However, carry over does decrease as the difference between the training and testing velocity increases. Training at 60 and 240°/sec also produces equivalent gains in isometric strength (Kraemer et al. 2000). A speed of 180°/sec sits in the middle of the spectrum of speeds available on isokinetic machines and, as such, represents the centre of the muscular strength to endurance continuum (Kraemer et al. 2000). Bearing in mind the carry over effect, training at 180°/sec could produce strength gains over a wide range of velocities (Kraemer et al. 2000).

FR or the ability to sustain maximal muscular force can also be improved with RT (see section above '*Fatigue'*), generally this is measured using the FI (ratio based upon initial and final muscle force).

2.3.2 Changes in muscle structure and function in healthy elderly subjects

Sarcopenia describes the age-related changes in muscle morphology that occur with ageing which lead to decreased muscle strength and mass (Cuthbertson et al. 2006;Dutta 1997). Muscle strength is known to decrease by 30-40% between the ages of 30 and 80 years (Young et al. 1984;Young et al. 1985) and this correlates with decreased mass (reduced fibre cross-sectional area). This decline may be associated with decreased physical activity (PA) during ageing (Jubrias et al. 1997).

There is some discrepancy in the literature regarding the effects of ageing on muscle fatigue. Some investigators suggest that older people experience greater muscle fatigue than younger counterparts (Cupido et al. 1992;Petrella et al. 2005). Petrella et al. found that peak isokinetic force fell by 24% after just 10 knee extensions in older adults [mean age 64 years (Petrella et al. 2005)]. This deficit persisted even after adjustment for muscle mass (lower in old age) and suggested that the force-velocity relationship changes with ageing (Petrella et al. 2005). Callahan and co-workers observed FR in young (24 years on average) and old (mean of 69 years) healthy individuals during three muscle fatigue protocols of the quadriceps (isometric, intermediate and high PAV contractions). The older subjects showed greater FR during the isometric test, less FR at the high PAV (240°/sec) and there was no difference between the age groups for the intermediate PAV contractions (Callahan & Kent-Braun 2011). Again this supports the notion that contractile velocity has an impact on force generated for age-related muscle fatigue. i.e. older

subjects exhibit more fatigue at high velocity strength testing and this affects muscle power [force x speed (Rawson 2010)].

However, there is the opposing argument that older people are more FR than the young because ageing muscle relays more heavily on oxidative rather than glycoltic pathways and therefore lactate production is reduced (Lanza et al. 2004). A recent study by Rawson et al. analysed fatigue for old (mean age 66 years) and young healthy men using the same isokinetic RT protocol described in this thesis [five sets of 30 knee extensions at 180°/sec, one minutes rest between sets (Rawson 2010)]. This protocol took place on one testing session rather than in the context of a RT programme. Both groups had significant reductions in absolute torque generation for sets 2-5 (compared to set one) and younger individuals produced significantly more torque on each set. The authors also calculated relative fatigue using a FI and found that relative fatigue was significantly greater in young subjects compared to the old ($p<0.001$). The overall relative fatigue (% decline in torque sets 2-5 compared to set 1) was 22.2% in the older men compared to 38.1% in the younger men. The authors of this study concluded that older men demonstrated enhanced FR during their chosen testing protocol which included intermittent contractions (approximately 30 seconds), interspersed with 60 seconds of rest. They argued that this type of testing favours the oxidative preferences of ageing muscle, as intermittent contractions favour the replenishment of oxygen within the muscle. Therefore varying testing methods and rest intervals is likely to influence FR.

Previous research has demonstrated that aging also alters the neuromuscular response to short-term disuse (two weeks of limb-immobilisation) and recovery in humans. For older individuals, immobilisation had a greater impact on neural motor function, while young individuals were more affected at the muscular level (fibre size atrophy). None the less, in this study (Suetta et al. 2009) and others, the age-related loss of strength and mass can be regained with exercise training and there is evidence that training adaptations may be greater in the elderly compared to younger individuals (Jubrias et al. 2001).

Muscle weakness and reduced power contributes to difficulty in transferring [e.g. rising from a chair (Alexander et al. 1997)] and an increased falls risk in this age group (Schultz et al. 1997). As such, RT should be advocated to improve muscle strength, power and mass. However there is more susceptibility for muscle damage during heavy RT, in older adults, and investigations have shown that muscle recovery/ repair is slower in older persons after RT (Roth et al. 2000).

The effects of ageing on the muscles of patients with COPD is largely unknown (American Thoracic Society/ European Respiratory Society 1999). It is unclear whether the decline in muscle function seen with normal ageing is more pronounced or accelerated in these patients.

2.3.3 Skeletal muscle dysfunction in COPD

Skeletal muscle dysfunction describes the selective loss of skeletal muscle mass and strength (Schols et al. 1991c). Observed changes in the muscle

include a loss of contractile proteins, reduced capillarity, decreased fat free mass and lower myoglobin levels (American Thoracic Society/ European Respiratory Society 1999;Decramer et al. 2005). Muscle fibre type composition is also known to change [relative reduction in the proportion of type I (oxidative) fibres and increased proportion of type IIb (glycolytic) fibres] as well as a lower fibre-to-capillary ratio (Hurley et al. 1986;Whittom et al. 1998). The reduction in type I fibres is associated with disease severity in terms of FEV_1 percent predicted (Vogiatzis et al. 2011). As such, quadriceps endurance is reduced in patients with COPD, compared to controls (Swallow et al. 2007a) and premature metabolite accumulation occurs (Saey et al. 2005).

The molecular mechanisms responsible for regulating skeletal muscle growth and atrophy in this population are not fully understood. However deconditioning through inactivity is undoubtedly involved (Decramer et al. 1994). Other proposed causes include systemic inflammation, nutritional depletion, hypoxaemia, oxidative stress and steroid-induced myopathy (American Thoracic Society/ European Respiratory Society 1999;Decramer et al. 2005). It may be that several mechanisms are responsible for skeletal muscle dysfunction in this population and that the relative contribution of factors may differ between patients.

Skeletal muscle mass is determined by the relative rates of protein synthesis (anabolic process) and protein breakdown (catabolic process). Therefore, skeletal muscle atrophy may be a consequence of a reduction in muscle

protein synthesis and/or an increase in protein breakdown (resulting in net protein loss). Several authors have found reductions in amino acid concentrations in patients with COPD when compared to control subjects (Pouw et al. 1998;Schols et al. 1993a;Schols et al. 1996;Yoneda et al. 2001) and there is some evidence of increased whole-body protein turnover (increased rates of protein synthesis and breakdown) in this group of patients compared to healthy controls (Engelen 2000). The reasons for this are still being elucidated but it is likely that protein synthesis and degradation rates are altered in patients with COPD due to changes in protein signalling pathways (Jagoe & Goldberg 2001).

Weight loss is an important feature in COPD, with many patients being undernourished. This has a negative influence on protein balance, particularly within the muscle (American Thoracic Society/ European Respiratory Society 1999). A commonly used definition of nutritional depletion is a body weight of less than 90% of ideal body weight. Based on this definition, 35% of patients entering pulmonary rehabilitation (PR) would be deemed nutritionally depleted (Schols et al. 1993b). Weight loss occurs when energy (caloric) expenditure (EE) exceeds energy intake from the diet (Kao et al. 2011). It should be remembered that for patients with COPD, their disability may present an obstacle in the purchase and preparation of food. This may also be related to social deprivation which is a risk factor for COPD (Hansel & Kon 2008). In addition, several investigators have shown that resting energy expenditure (REE) is elevated in patients with COPD (Creutzberg et al. 1998b;Schols et al. 1991a); further exacerbating weight loss and may relate to greater energy

demands imposed by the increased work of breathing and certain medications (Creutzberg et al. 1998a;Palange et al. 1995). In acute exacerbations, REE is likely to be further increased (Vermeeren et al. 2004).

Importantly, subjects of normal weight may show a relative loss of muscle (fat-free) mass [FFM (Schols et al. 1991c)]. Reduced FFM is associated with the degree of airflow obstruction (Ischaki et al. 2007). Cachexia (defined as a low BMI and low FFM) is most prevalent in GOLD stage IV (Schols et al. 2005). A loss of FFM is associated with reduced muscle strength (Engelen et al. 1998) and increased morbidity (Bolton et al. 2004). Furthermore, FFM depletion correlates with walking performance (Schols et al. 1991b), maximal oxygen uptake (Baarends et al. 1997a) and adversely affects health status (Mostert et al. 2000;Shoup et al. 1997). The loss of bone mineral density (BMD) is also common in patients with COPD and this has been linked to reduced FFM (Bolton et al. 2004)

Alterations in muscle structure and function mirror that of other chronic diseases, such as heart failure (Gosker et al. 2000) and in immobilising conditions of healthy subjects. Disuse and unloading of the muscles is associated with reductions in protein synthesis and increases in degradation (Ferrando et al. 1996b;Gibson et al. 1987). Some novel research conducted at the University of Nottingham in 2004 found that by immobilising healthy young men in a limb cast for two weeks, a five percent decrease in quadriceps strength was linked to altered expression of several candidate genes [figure 2.2 (Jones et al. 2004)]. Following a carefully controlled RT programme,

muscle mass and strength returned to basal levels and again this was linked to changes in gene expression (figure 2.2).

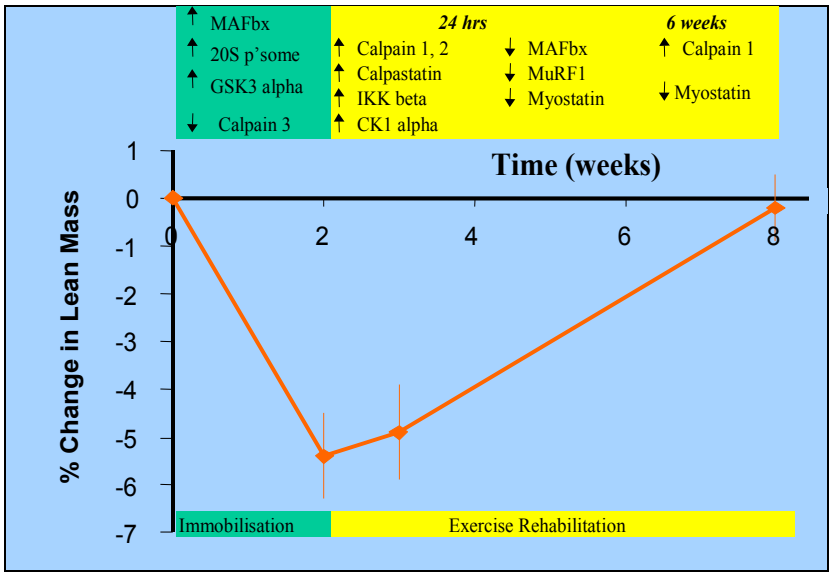


Figure 2.2 Overview of changes in quadriceps lean mass and targeted gene expression during 2 weeks of limb immobilisation and 6 weeks of prescribed rehabilitation exercise in healthy male volunteers.

These study findings (Jones et al. 2004) suggested that at least part of the loss of muscle mass in immobilising conditions, such as COPD, may be linked to gene activation. This concept provided the basis of the larger MRC funded study, described in this thesis.

2.3.4 Consequences of skeletal muscle dysfunction

Skeletal muscle dysfunction is now recognised as an important factor in the exercise limitations of this population (American Thoracic Society/ European Respiratory Society 1999;Decramer et al. 2005;Gosselink, Troosters, & Decramer 1996) and contributes to whole-body exercise performance (Gosselink, Troosters, & Decramer 1996;Steiner et al. 2005). We have known for a number of years that patients with COPD are weaker than healthy

counterparts of the same age (Bernard et al. 1998;Hamilton et al. 1995). Both upper and lower-limb muscle force are reduced, although the muscles of ambulation are the most affected (Bernard et al. 1998;Man et al. 2003b).

Muscle weakness and atrophy are important variables to measure because they are better prognostic indicators than lung function (Marquis et al. 2002; Swallow et al. 2007b). Quadriceps weakness is also associated with higher health care utilisation (Decramer et al. 1997b). Furthermore, the skeletal muscles may provide a target for treatment in an otherwise irreversible lung disease.

We are aware that patients with COPD experience greater muscle fatigue than healthy, age-matched controls ($p<0.01$) and that their rate of fatigue is more rapid (Allaire et al. 2004;Swallow 2007a), which causes patients to cease exercise prematurely. Fatigue has been defined in various ways in the literature for patients with COPD. This makes it difficult to compare studies and to generate an agreed definition. Allaire and colleagues described isometric muscle *endurance*; this was significantly lower in patients with COPD compared to controls ($p<0.001$) and that this was linked to reduced markers of muscle oxidative metabolism [type I fibres and oxidative enzymes (Allaire et al. 2004)]. Using magnetic stimulation of the intramuscular branches of femoral nerve, Swallow and colleagues found that the time taken for quadriceps force to fall to 70% of baseline (their definition of fatigue) was significantly shorter in patients with COPD (55.6 seconds) compared to the control group (121 seconds, $p<0.01$). The same authors also measured

quadriceps twitch force (TwQ) before and 10 minutes after this endurance protocol. Half of the patients with COPD showed evidence of fatigue using a 15% reduction in TwQ force criteria. None of the control subjects met this criterion. Two previous studies also found that 50% of patients with COPD experience this post-exercise fall in TwQ (Mador et al. 2003;Saey et al. 2003a). Saey et al found a significant relationship between the fall in TwQ with lactate levels and capillary/ fibre ratio; suggesting that the skeletal muscle changes which occur in COPD lead to a higher reliance on anaerobic glycolysis during exercise. This causes premature acidosis and is linked to aerobic muscle fatigue (Saey et al. 2005).

Muscle fatigue, and particularly the FI, is seldom reported in studies of patients with COPD. In one study were the FI is reported, subjects were asked to perform the maximum number of knee extensions possible in one minute (at an isokinetic PAV of 70°/ sec) before and after a neuromuscular electrical stimulation (NMES) training programme (Neder et al. 2002). The FI was calculated as the ratio between the work performed in the last and first three contractions (%); therefore a lower number indicates greater fatigue resistance. There was a significant reduction in the FI from a mean of 113.7 % prior to the NMES programme, to 74.9% after NMES. However this study only included 9 subjects, therefore variation between individuals was high and subjects were not familiarised to the fatigue protocol, therefore a learning effect may have occurred on repeat testing.

2.4 Treatments used in patients with COPD

This section appraises current treatments for patients with COPD. These options are comprehensively described in the most recent NICE guidelines for COPD (National Institute for Clinical Excellence 2010).

2.4.1 Pharmacology

Bronchodilators represent the basis of pharmacological COPD management. Three types are available: beta$_2$ agonists, antimuscarinics and theophylline. All three relax airway smooth muscle but are activated via different pathways (Carrera et al. 2008). Short-acting versions of these drugs work quickly to relieve breathlessness and may increase exercise tolerance by improving inspiratory capacity (Newton et al. 2002). In patients with stable COPD who remain breathless, despite the use of a short-acting bronchodilator, the following maintenance options are available:

- if FEV_1 is ≥ 50% predicted, offer either a long-acting beta$_2$ agonist (LABA) or long-acting muscarinic antagonist (LAMA),
- if FEV_1 is <50% predicted, offer either a LABA with an inhaled corticosteroid (ICS) or LAMA (National Institute for Clinical Excellence 2010).

The same is true of those who experience frequent AE (National Institute for Clinical Excellence 2010).

2.4.2 Surgery

Surgery for individuals with COPD is rare and is only offered to a minority of patients who fulfil strict criteria. Lung Volume Reduction Surgery (LVRS) is becoming increasingly popular for patients with localised areas of emphysema. The procedure involves removing a poorly functioning area of lung so that the remaining lung has more 'room' to work efficiently (Department of Health 2010). Much of our knowledge around LVRS stems from the National Emphysema Treatment Trial (NETT) which compared optimal medical management (including rehabilitation= control) and optimal medical management plus LVRS (Weinmann et al. 2008).]. At long-term follow-up (median 4.3 years), total mortality rates were 0.11 deaths per person per year in the LVRS group and 0.13 in the control group [p=0.02 (Criner et al. 2011)].

2.4.3 Oxygen therapy and ventilation

The aim of oxygen therapy is to provide the necessary amount of oxygen to all bodily tissues (PaO_2 of at least 8.0kPa or to improve oxygen saturation to at least 90%), this ensures perfusion of vital organs (Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2009). Oxygen can be delivered by concentrators, gas cylinders or in liquid form, depending on the patients' requirements (Bradley et al. 2007;Lee and Kon 2010). Patients with chronic hypoxaemia (PaO_2 <7.3kPa) benefit from long-term oxygen therapy (LTOT), delivered for at least 15 hours per day (Calverley and Walker 2003;Department of Health 2010). LTOT is known to increase survival in

hypoxic COPD patients (Calverley & Walker 2003), probably by reducing the rate of pulmonary arterial hypertension development (Lee & Kon 2010).

Other patients may only require ambulatory oxygen therapy (AOT) if they have significant oxygen de-saturation on exertion (fall in oxygen saturation of 4% to below 90%). AOT can acutely improve exercise tolerance and reduce dyspnoea at sub-maximal work rates (Bradley et al. 2007;Lee & Kon 2010;Nonoyama et al. 2007). However, a recent paper has challenged the use of exercise de-saturation as the primary criterion for AOT prescription (Moore et al. 2011). Their results found that those with oxygen de-saturation after a six-minute walk test (6MWT) did not derive benefit from using oxygen on subsequent testing.

Non-invasive ventilation (NIV) should be used as the treatment of choice for persistent hypercapnic ventilatory failure (American College of Chest Physicians 1999) and during AE which are not responding to conventional medical therapy (National Institute for Clinical Excellence 2010). NIV delivers positive airway pressure and works by ‘offloading’ the respiratory muscles during exercise, allowing patients to train at higher intensities and thereby enhancing performance (Garrod et al. 2000;Johnson et al. 2002).

2.4.4 Pulmonary rehabilitation (PR)

PR is defined as: ‘an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. PR is designed to

reduce symptoms, optimise functional status, increase participation, and reduce health-care costs through stabilising or reversing systemic manifestations of the disease' (Nici et al. 2006). These goals are accomplished by helping patients become more physically active (Department of Health 2010) whilst learning more about their disease. Comprehensive PR programmes include patient assessment, exercise training, education, and psychosocial support' (Nici et al. 2006a) and should be available to all COPD patients who have a functional limitation (Department of Health 2010), including those who have recently been hospitalised for an exacerbation (National Institute for Clinical Excellence 2010).

PR programmes typically last between six weeks (UK) and 6-months (Europe) and can be effectively delivered within a variety of settings (Troosters & Decramer 2008). The benefit of supervised over unsupervised exercise has been demonstrated in controlled studies (Lacasse et al. 2006;Puente-Maestu et al. 2000) but for logistical reasons many programmes combine weekly or twice weekly supervised sessions with additional home exercises. In England, programmes typically run twice a week for six to 12-weeks (Department of Health 2010). However there is no real consensus about the optimum duration of a PR programme. Significant improvements in exercise tolerance and health related QoL (HRQoL) have been shown in programmes as short as ten days (Votto et al. 1996) and as long as 18-months (Wijkstra et al. 1995). Shorter programmes clearly decrease the cost per patient and disperse limited resources amongst more people (Clini et al. 2001) but long-term behaviour change may be facilitated by a longer treatment exposure (Ries et

al. 2007). Sewell and colleagues (Sewell et al. 2006) observed that a shortened 4-week supervised PR programme was equivalent to a 7-week supervised PR programme at the comparable time points of 7-weeks and 6-months. Outcomes assessed were exercise tolerance and disease-specific QoL. It may be that the duration of the programme can be dictated by the patients' needs.

PR should include exercise training for the muscles of ambulation (Ries et al. 2007). Lower-limb aerobic training (e.g. walking or cycling) should be at an intensity of between 60-80% of the peak work achieved on a maximal exercise test (Casaburi et al. 1991;Maltais et al. 1997). Training load progression can be achieved by increasing exercise duration whilst keeping intensity constant (Singh et al. 1998) or by increasing intensity when the optimum duration has been attained (Griffiths et al. 2000a); both approaches are effective. Training intensity can be monitored using Borg breathlessness and perceived exertion scales (Borg 1982). Typically, as patients improve, they will achieve the same Borg rating at a higher absolute work rate (Troosters & Decramer 2008). Heart rate (HR) may also be used to establish training intensity. Maximal HR is calculated as 220 – age, and a HR of 65 to 85% of maximum relates to the target training zone for cardio-respiratory fitness (Tanaka et al. 2001).

Modifications can be made to conventional whole-body exercise training to overcome ventilatory limitations in patients with severe disease. These include alleviating the work of breathing (supplemental oxygen or NIV), reducing the

muscle mass at work (e.g. single leg cycling) and shortening the time of training bouts [interval training (Troosters & Decramer 2008)]. Interval training has been found to confer equivalent benefits to continuous training in a recent systematic review (Beauchamp et al. 2010).

RT for the peripheral muscles should also be included to improve skeletal muscle function (Troosters & Decramer 2008). This approach is discussed further in section 2.5.1.

Patient education is the other key component of PR. Discriminating between the effects of education and exercise is difficult as they are generally administered together (Nici et al. 2006b). Studies which have compared comprehensive PR with education alone demonstrate that education alone has no independent benefit (Ries et al. 2007). Education can be delivered in a number of ways and, in general, the topics covered are: disease education, exacerbation management, medications, managing breathlessness, chest clearance and lifestyle advice [smoking cessation, healthy diet, promoting PA, energy conservation]. Amongst the potential benefits of education are: active participation in healthcare and increased coping skills (Von et al. 1997). Two disease-specific knowledge questionnaires have been developed which can help to identify knowledge deficits in patients with COPD and their carers. They are the LINQ [Lung Information Needs Questionnaire (Jones et al. 2008)] and the BCKQ [Bristol COPD Knowledge Questionnaire (White et al. 2006)]. By identifying gaps in knowledge; individualised education can be delivered. The LINQ is known to be sensitive to change following PR (Jones

et al. 2008). There continues to be limited research about the impact of education on the outcomes of PR in patients with COPD, such as increased PA but expert opinion suggests that there are important benefits of patient education (Ries et al. 2007).

The exercise component of PR has consistently been found to improve exercise tolerance, muscle strength and endurance. These impressive changes, in exercise performance, are seen in the absence of lung function improvements (American Thoracic Society/ European Respiratory Society 1999) and support the notion that PR targets the extra-pulmonary consequences of COPD.

Bolton and co-workers found that quadriceps strength and FFM improved after an 8-week in-patient PR programme (Bolton et al. 2007). However the gains in FFM returned to basal levels 4-weeks after the cessation of PR, when the anabolic stimulus of exercise had stopped (Bolton et al. 2007). A recent study (Vogiatzis et al. 2011) has shown that PR [interval training (cycling)] can also influence fibre type distribution and capillary-fibre ratio within the muscle, as evidenced by sampling vastus lateralis muscle biopsies. The changes were comparable across the gold stages. Furthermore, PR helps to address the cardiovascular risk factors associated with COPD by reducing blood pressure (and therefore arterial stiffness) and cholesterol levels (Gale et al. 2011).

PR also enhances HRQoL in patients with COPD (Ries et al. 2007), reduces hospital days (Griffiths et al. 2000b) and decreases yearly hospitalisation and

exacerbation rates (Foglio et al. 2001). This may be potentially cost-effective (Griffiths et al. 2001).

2.5 Interventions explored in this thesis

2.5.1 Resistance training (RT)

The skeletal muscle alterations displayed in patients with COPD, indicate that muscle training should play an important role in the treatment of this patient group (O'Shea, Taylor, & Paratz 2004). RT is appealing as it is the optimum form of exercise to increase muscle mass and strength in healthy and diseased populations (Brown et al. 1990a;Nici et al. 2006). Given the problems of muscle weakness and wastage in patients with COPD, guidelines recommend that RT should be included in a PR programme (Ries et al. 2007). Despite these recommendations, relatively few published studies have explored the role of RT in COPD (Alexander et al. 2008).

The single systematic review on RT in COPD (O'Shea, Taylor, & Paratz 2004) yielded only 13 articles, four of which were previous reviews. In the nine experimental studies, training sessions generally included two to four sets of six to 12 repetitions of each strength exercise at 50% to 85% of an individuals' one repetition-maximum [(1RM) defined later in this section. Training programmes were, on average, eight to 12-weeks in duration at a frequency of two or three times per week, with individual sessions lasting between 40 and 90 minutes. These training regimes were generally in line with guidelines for healthy adults (Kraemer et al. 2002), and reflect what was subsequently

published in the ATS/ ERS Statement on PR (Nici et al. 2006c). Many of the programmes included combined endurance and RT; therefore the relative value of RT in isolation was difficult to establish. The authors of this review concluded that peripheral RT was feasible and safe for patients with COPD, even at intensities of 80% and beyond of the pre-training 1RM (Bernard et al. 1998;Simpson et al. 1992). No adverse events were reported, although the teaching of the correct lifting technique is important to avoid breath holding in these patients (Storer 2001).

We know that in healthy adults, symptom scores have a linear relationship with RT intensity [i.e. as intensity increases, symptom scores increase (Pincivero et al. 2001)]. The symptoms of dyspnoea and perceived exertion, in patients with COPD, are significantly lower during RT when compared to during whole-body exercise performance (Probst et al. 2006).

This meta-analysis suggested that RT had a positive effect on both upper limb and knee extensor strength ($p < 0.001$) and lower-limb muscle mass (O'Shea, Taylor, & Paratz 2004). However, the impact of RT on other outcome measures, such as health status and PA, was less clear. For this reason, the authors later updated their review (O'Shea et al. 2009b) with an emphasis on activity and participation level outcomes. This second review yielded 10 additional trials and again the authors were able to conclude that progressive RT lead to appreciable increases in muscle strength compared to control or aerobic training. Interestingly, meta-analyses found large effect sizes for increases in leg press strength (weighted mean change 16.2%, δ 0.96,

p=0.006) and only small effect sizes for upper limb strength improvements. This can be expected as upper-limb strength is thought to be relatively well preserved in patients with COPD, compared to lower-limb strength (Bernard, Leblanc, Whittom, Carrier, Jobin, Belleau, & Maltais 1998;Gosselink 2002;Hamilton, Killian, Summers, & Jones 1995) and would therefore have less scope to change. Four studies included in the review (Kongsgaard et al. 2004;O'Shea et al. 2007a;Panton et al. 2004;Phillips et al. 2006) suggested that improvements in strength may carry over to daily task performance such as stair climbing and rising from a chair. However there were inconsistencies in the outcomes between the studies and a greater risk for bias which could have overestimated the effect size (O'Shea, Taylor, & Paratz 2009b). Isolated RT can also lead to increases in whole-body exercise (endurance) performance, albeit to a lesser extent than endurance training (Vonbank et al. 2011).

RT may also offer advantages in patients with severe disease; where ventilatory limitation is often the main contributor to exercise intolerance. i.e. patients terminate exercise because they are unable to increase ventilation in response to growing metabolic demands (O'Donnell 2001). There is a school of thought, that for more disabled patients with COPD; RT of small muscle volumes may allow for higher training intensities at a muscle level than traditional whole-body exercise. This is important for patients disabled by COPD who are ventilatory limited (Simpson et al. 1992). Probst and co-workers have shown that cardiopulmonary stress/ metabolic load is lower in resistance exercise when compared to endurance training at the start, middle

and end of a 12-week training programme (Probst et al. 2006). This was observed in both objective (e.g. minute ventilation, oxygen uptake derived from a portable breath by breath system) and subjective (i.e. symptom scores) parameters. The HR response after leg press exercise was significantly lower than walking, cycling (week 1 and 6 only) stair climbing and arm cranking. Subjects also experienced less dyspnoea during leg press exercise compared to cycling (weeks 1, 6 and 12 $p<0.05$). More recently, Sillen *et al* found that the metabolic response was significantly lower still with neuromuscular electrical stimulation (NMES) compared to RT during a single session (Sillen et al. 2008). Peak oxygen uptake (as a percentage of the maximum) was 57% for RT and 34% for NMES ($p<0.001$ between RT and NMES) and Borg dyspnoea scores were 3 (RT) and 1 [(NMES) $p<0.01$ between groups]. However, the authors concluded that both NMES and RT resulted in acceptable metabolic responses and symptom scores for patients (Sillen et al. 2008).

Unlike endurance training, we do not know what the optimum 'dose' of RT is, to derive maximum benefit in terms of muscle strength and mass. The 'dose' comprises of training intensity and duration (Zuwallack et al. 2006). The relationship between RT intensity and outcome measures, such as strength and mass have been poorly described. Ideally, the optimum 'dose' of training should depend on the individuals' needs and the ongoing measurement of outcomes during training (Ries et al. 2007). However the serial measurement of outcomes may be impractical in the context of a PR programme and programmes are generally a fixed length due to resource constraints.

ZuWallack and co-workers took serial measures every four sessions during a 24 session rehabilitation programme [bi-weekly for 12-weeks (Zuwallack et al. 2006)]. Outcomes assessed were: treadmill endurance time (at 85% of maximum work rate), upper-limb endurance lifts, Borg dyspnoea levels (at isotime on the treadmill test) and HRQoL. All outcomes improved significantly from baseline as early as session four. Upper- and lower-limb endurance outcomes continued to improve until session 20, when a plateau was noted. We do not know whether changes in muscle strength and mass, following RT, track the same trajectory as improvements in exercise tolerance and HRQoL derived from comprehensive PR, in patients with COPD. The dose-response relationship of RT has, however, been explored in healthy individuals (Rhea et al. 2003). The authors found, that for untrained individuals, 80% of the 1RM was the most effective to elicit changes in strength and training should include four sets per muscle group, three times per week. A meta-analysis, including 1313 older subjects (age range 65-81 years) found that progressive RT improved maximal strength in a dose-dependant pattern (Steib et al. 2010). The authors concluded that more research was still required to refine the optimum training parameters in old/ frail populations.

RT can be prescribed in a number of ways and manipulation of training variables (e.g. number of sets/ repetitions and level of resistance) can stress the muscles in different ways to produce specific adaptations. DeLorme was the first to suggest that a RT programme with low repetitions and high resistance would favour improvements in strength (DeLorme 1945). Most RT programmes in research studies use a percentage of the 1RM to establish a

training load; ≥ 70% would be typical for RT in all populations. The 1RM is defined as the maximum amount of weight that can be lifted with the proper technique for one repetition only (Baechle et al. 2008). Alternatively loads can be assigned by a given number of repetitions (Baechle et al. 2008). For example, if an individual can lift 20 kilograms (kg) for ten repetitions, their 10RM is 20kg. Using RM training loads is appropriate for machine weights or free weights and three sets of eight repetitions is sufficient to elicit a training response in patients with COPD (Spruit et al. 2002). Clearly as the percentage of the 1RM decreases, the subject should be able to perform more repetitions (Baechle, Earle, & Wathan 2008). However other modes of resistance are available including isokinetic dynamometry (see section 2.3.1 *muscle contraction mechanism and types of contraction*), elastic resistance bands and using body weight (callisthenics). RT is generally progressed by increasing the resistance/ weight, whilst keeping the number of sets and repetitions the same (i.e. low).

Motivation for exercise (including RT), theoretically has a significant influence on exercise performance and progression. Motivation is defined as: 'the process that initiates, guides and maintains goal-oriented behaviours.' This can be intrinsic (from within, e.g. enjoyment of exercise) or extrinsic [e.g. financial rewards (Vallerand 1999)]. There are several questionnaires which aim to determine an individuals' general motives for exercising. For example, the *Exercise Motivations Inventory-2* [EMI-2 (Markland and Ingledew 1997)]. One assumes that motivation for RT, on a session by session basis, is reflected in a participants' exerted effort. This is often measured in patients

with COPD using the Borg RPE scale (Borg 1982), outlined previously and displayed in appendix 9. There is a strong dose–response relationship between RT intensity and strength gains, therefore high-intensity (or high-effort) training produces greater improvements in performance compared to low-intensity (low-effort) training (Fatouros et al. 2005;Seynnes et al. 2004). We are aware, from previous literature, that high motivation and particularly high intrinsic motivation, is associated with greater exercise adherence. Furthermore, high post-exercise enjoyment ratings are also related to greater continued adherence with exercise (Ryan et al. 1997) which has a positive effect on training outcomes [e.g. strength (Winett et al. 2009)].

Preservation of strength following resistance training

Although the short-term benefits of RT are clear (Lacasse et al. 2006;O'Shea, Taylor, & Paratz 2004;Ortega et al. 2002), we know very little about whether strength gains are sustained in the long-term for patients with COPD. In fact, even in healthy older adults there is limited information about how long the benefits from strength training are maintained. Various authors have proposed that strength may be sustained for anything from five to 32 weeks once training ceases in healthy older adults (American College of Sports Medicine 1998;Fatouros et al. 2005;Hakkinen et al. 2000;Lemmer et al. 2000;Taaffe and Marcus 1997).

A comprehensive literature search was undertaken as part of this thesis to establish the knowledge regarding the long-term preservation of strength following RT in patients with COPD (Houchen et al. 2009). Despite an

extensive search of the literature, only four studies were located [(O'Shea, Taylor, & Paratz 2007a;Ortega et al. 2002;Troosters et al. 2000;van Wetering et al. 2010). Although RT is a key feature of many longitudinal PR studies, it appears that strength is rarely measured as an outcome at follow-up. One of the studies included in the review suggested that strength gains remain statistically higher than baseline, 12-months following graduation from a six-month training programme (Troosters, Gosselink, & Decramer 2000). It was not possible to pool the results of the four studies statistically, as the study interventions and assessments were heterogeneous. Furthermore, the four papers reported conflicting findings. A PDF of the narrative review findings and details of the four included studies can be found in appendix 1 (the data from van Wetering et al. was published after the review publication).

The four studies included in the review measured the long-term sustainability of strength following fairly lengthy PR programmes (12-weeks to 6-months). The preservation of strength after a short course of RT (i.e. a 7-week programme) is unknown. Therefore, as part of this PhD programme, I analysed the 6-month follow-up strength data from a previous RCT conducted at the University Hospitals of Leicester (UHL) NHS Trust. Participants had attended a 7-week outpatient PR programme, enhanced with individualised RT (Deacon et al. 2008). This involved 21 sessions utilising multi-gym machines for leg extensions, step-up and sit-to-stand exercises (all 3x8 repetitions). Isometric quadriceps strength was assessed at baseline (after familiarisation), immediately after rehabilitation and at 6-months using an isokinetic dynamometer. Quadriceps strength increased significantly after the

7- week course of PR and remained significantly higher than baseline at 6-months. This was in the absence of a formal maintenance programme. The full PDF report can be found in appendix 2.

RT may prove more challenging to continue at home after PR (compared to endurance walking), due to lack of access to specific equipment (e.g. multi-gym machines or free weights). Feasible ways to continue strength training within the home require further exploration.

2.5.2 Nutritional supplementation

Nutritional supplementation in the context of COPD serves a dual purpose: to increase body weight and to enhance exercise performance. I shall discuss these two goals in the following section.

It is a widely accepted that under nourished patients with COPD should receive nutritional supplementation (American Thoracic Society/ European Respiratory Society 1999). Re-feeding trials in malnourished patients have been shown to improve nutritional status and respiratory muscle strength (Whittaker et al. 1990;Wilson et al. 1986). Calorific supplementation, principally protein, may be particularly necessary during an exacerbation to prevent muscle wastage (Vermeeren, Wouters, Geraerts-Keeris, & Schols 2004). Three placebo-controlled studies of oral nutritional support in stable patients were able to show improvements in body weight and functional performance at four to eight weeks (Efthimiou et al. 1988;Rogers et al. 1992;Whittaker et al.1990). However these benefits have not been universal

and a Cochrane review of nutritional supplementation in COPD came to disappointing conclusions (Ferreira et al. 2005). Studies in this remit have generally included small numbers and have been difficult to compare due the heterogeneity in the patient population, setting, supplementation composition and outcome measures.

The overriding message appears to be that nutrition in isolation is not effective. In particular, those with evidence of systemic inflammation respond particularly badly (Creutzberg et al. 2000). Furthermore the effects of supplementation may be negated by patients who reduce their normal dietary intake (Knowles et al. 1988) or fail to comply due to the gastro-intestinal side effects of the supplement. It may be that a stimulus, such as exercise is needed to increase appetite and a few studies have explored the use of supplements alongside generic PR. Schols and colleagues investigated the effects of a daily nutritional supplement (mainly fat) alongside an 8-week rehabilitation programme (Schols et al. 1995). This study saw improvements in anthropometric measures (e.g. body weight, fat free mass) and respiratory muscle strength (maximal inspiratory pressure: PImax), but no additional increase in exercise performance. In post-hoc survival analysis, those who achieved significant weight gain (>2kg in 8-weeks) and had an increased PImax during PR, had a better chance of survival (Schols et al. 1998).

A study by Steiner et al. utilised carbohydrate supplements. The authors found that only the well-nourished sub-group had significantly greater improvements in shuttle walk test performance and the magnitude of the

increase correlated with total carbohydrate intake [r=0.46, p=0.001 (Steiner et al. 2003)]. It may be that PA or exercise could be costly in terms of energy for COPD patients; contributing to a negative energy balance in weight-losing patients. A poor treatment response to nutrition in these weight-losing patients may be attributed to an inadequate assessment of their energy requirements (Baarends et al. 1997b), particularly when engaged in a rehabilitation programme.

Recently, Pison and co-workers have investigated the efficacy of a multimodal nutritional rehabilitation programme in malnourished patients with respiratory failure [LTOT and/ NIV (Pison et al. 2011)]. 122 patients were assigned to the multimodal nutritional rehabilitation programme (rehab) or the home-based education (control) group. Rehab comprised of oral testosterone, three nutritional supplements per day (20% protein, 60% carbohydrate, 20% lipids) and exercise for 90 days. Exercise was endurance cycling and RT with elasticised bands. After the 90 day trial period, patients in the rehab group had significant improvements in body composition (BMI, FFM), peak workload, cycle endurance time and isometric quadriceps strength; compared to controls. After 450 days of follow-up, exacerbation rates and hospital admission rates were similar between groups but survival was significantly improved for the rehab group. The results of this multimodal intervention are encouraging but need to be confirmed in a larger study, in less severe patients and with a longer follow-up period. It appears that the combination of nutritional support with anabolic (muscle protein building) substances may be of value to undernourished patients and should be explored.

Dietary protein has been shown to induce protein synthesis in healthy young adults. However there appears to be an impaired response in healthy elderly subjects and merely providing dietary protein may not be effective in increasing protein synthesis (Cuthbertson et al. 2005), even when high doses of amino acids are ingested (highest titrated dose= 40 grams: g/ 500 millilitres: mls). Blood and biopsy markers were examined for evidence of protein synthesis in this study of 20 young and 24 elderly men. All subjects were mobile but not well trained (Cuthbertson et al. 2005). The authors found that the signal from protein ingestion is not 'sensed or transduced' as well by old muscle as it is in young muscle, resulting in a lower rate of protein synthesis to the same nutrient level delivered (Cuthbertson et al. 2005). It might be that an anabolic stimulus, such as exercise is needed.

The timing of supplementation in relation to RT may also be an important factor in the response for older people. As stated previously, protein synthesis after a bout of RT is known to be greater three hours post-training when compared to 24 and 48-hours later (Phillips, Tipton, Aarsland, Wolf, & Wolfe 1997). As protein availability is essential for optimum protein synthesis; the early intake of protein after RT is potentially important. Data from Denmark has shown that muscle hypertrophy (quadriceps CSA increase of 7%) only occurred in an elderly group receiving protein immediately after RT (36 sessions) and not in those receiving the protein two hours later [$p<0.001$ between timing groups (Esmarck et al. 2001)]. The supplement comprised of 10g of protein and 7g carbohydrate dissolved in water.

The role of protein given immediately after RT has not before been studied in the COPD population.

2.6 Measures used to assess the response to resistance training and nutritional supplementation

2.6.1 Quadriceps muscle strength

The aims of measuring muscle strength are: to identify and quantify impairment, to prescribe an appropriate exercise regime and to evaluate response to treatment (Storer 2001). Prior to measuring strength, several factors should be considered. One aspect to consider is familiarisation, which is, performing a practice of the actual testing manoeuvres before the actual testing. Otherwise, subjects who are naive to the testing method may improve strength scores on subsequent testing by simply getting better at doing the test ('learning effect.') This is particularly important when using unfamiliar/ unnatural testing methods (Brown & Weir 2001). After familiarisation, the actual testing should take place once muscle soreness is resolved [e.g. two-three days later (Brown & Weir 2001)]. Correct subject positioning and stabilisation of other joints/ muscles will also help to improve the accuracy of strength testing (Brown & Weir 2001). To decrease between operator variability, standardised instructions should be given to all subjects. Ideally the same operator should perform all measurements at the same time of day, each time, to reduce variability.

Strength can be measured using volitional or non-volitional techniques (Menon & Steiner 2009). Volitional techniques require maximum effort by the subject and can be affected by operator encouragement. Non-volitional testing using nerve stimulation is not effort dependant. Volitional strength can be assessed using static (isometric) or dynamic (isotonic/ isokinetic) contractions (see table 2.3) and measured manually, using resistance machines, with portable devices [e.g. handheld dynamometers (HHD), cable tensiometers] and using computerised dynamometers.

When the length of a muscle changes in response to stimuli, the term for the contraction is isotonic (Davies, Heiderscheit, & Brinks 2000). There are two types of isotonic contractions: concentric, in which the muscle actively shortens whilst overcoming external resistance and eccentric, in which the muscle actively lengthens whilst being overcome by an external resistance (Dvir 2004). Eccentric contractions occur to control movement against an applied force. e.g. when the elbow flexors must be active to control the fall of an object (Davies, Heiderscheit, & Brinks 2000).

When the length of the muscle doesn't change because of an externally applied force; then tension in the muscle increases in an attempt to overcome resistance. These static contractions are termed isometric (Palastanga, Field, & Soames 2006). Isometric contractions are preferred when trying to minimise the influence of neural components associated with muscle strength (Broughton 2001). Isometric contractions are quick and easy to perform and have shown to be highly reliable [correlation coefficients between 0.85 and

0.99 (Abernethy et al. 1995)]. However the strength recorded is specific to the point in the range of movement (ROM) at which the contraction occurred. If the joint angle is changed, then isometric strength is likely to change (Brown & Weir 2001). Furthermore, isometric testing may not reflect the dynamic nature of everyday tasks. There are no specific guidelines outlining the correct joint angles, the number of repetitions, rest period or duration of contraction for isometric testing. However several authors have made recommendations on these factors. It has been suggested that testing should take place at the joint angle associated with the greatest force production. For knee extension, the angle of greatest force production would be midway between full knee flexion and extension [approximately 65 degrees (Kulig et al. 1984)]. Literature suggests that contractions with a one second transition period and a plateau of four to five seconds should be sufficient to observe a maximal isometric contraction. Rest between repetitions should be one to five minutes (Brown & Weir 2001). Edwards and colleagues were amongst the first to explore the number of isometric repetitions required (Edwards et al. 1977). They suggested that three was sufficient given that the first was usually tentative and the last two were comparable to each other (coefficient of variation= 2.8%). More repetitions clearly increases the chance of fatigue and injury (Brown & Weir 2001)

Isokinetic contractions describe those in which there is an accommodating resistance and a fixed speed (Davies, Heiderscheit, & Brinks 2000). As the subject increases force, the dynamometer increases resistance to maintain the pre-defined set speed (Gaines & Talbot 1999). As such these contractions

can only be produced with specialised equipment (isokinetic dynamometers). The test re-test reliability of isokinetic testing is known to be very high from several studies (Frontera et al. 1993;Gleeson and Mercer 1992) and a wide range of variables can be analysed from the data collected. Peak torque is one variable of interest and is the product of mass, acceleration and level arm length (the peak of the torque versus the position curve- see figure 2.3). The maximum or peak torque can be produced anywhere within the range of ROM and is synonymous with the 1RM (Brown & Weir 2001). Work is a product of torque and distance travelled; this is the cumulative ability of the subject to produce torque throughout the ROM (the area under the curve- figure 2.3).

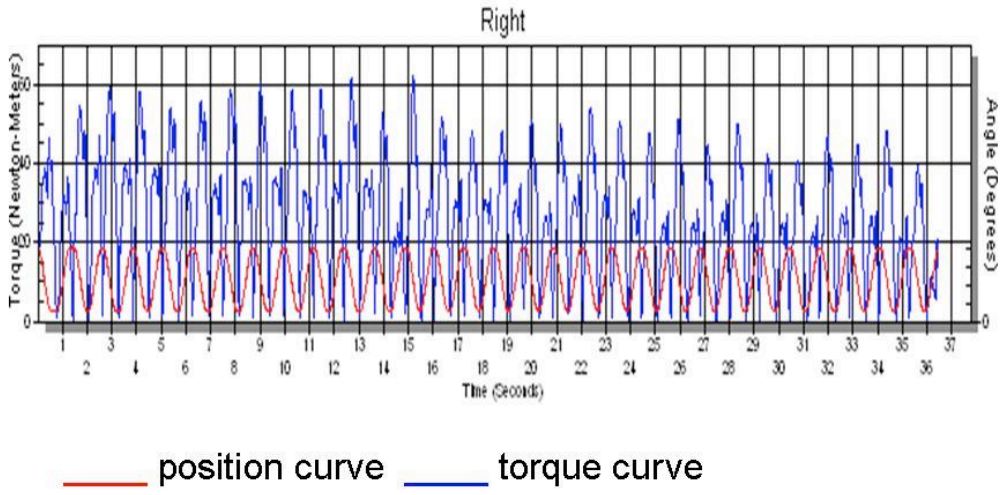


Figure 2.3 Isokinetic torque versus position graph

The number of repetitions chosen for isokinetic testing is dependant upon the outcome desired. Generally five repetitions are enough when measuring strength, as many as 50 may be performed when endurance is the outcome of interest (Brown & Weir 2001).

Isokinetic testing is unfamiliar to most individuals and is rarely used in the assessment and training of individuals with COPD. Only 16 out of 139 articles relating to RT in patients with COPD used an isokinetic dynamometer to measure dynamic strength (Robles et al. 2011). This systematic review found that most studies measured quadriceps strength at 60°/sec. Reliability results from isokinetic testing in the healthy population can not be easily extrapolated to patients with COPD who have weaker muscles and are more prone to fatigue (American Thoracic Society/ European Respiratory Society 1999). The test re-test reliability of isokinetic muscle testing has therefore been explored in patients with COPD. In 2004, Mathur and colleagues reported within-session and test re-test reliability over seven days for isokinetic strength testing in 20 patients with moderate to severe COPD (Mathur et al. 2004). Isokinetic testing of the quadriceps took place on the dominant leg for three trials at PAV's of 30 and 90 deg/ sec (°/sec). The within-session test re-test reliability was high [intra-class correlation co-efficient (ICC) ranging from 0.95 (90°/sec) to 0.99 (30°/sec)]. There were no significant differences between the three trials ($p>0.05$). There were also no significant differences between the peak torque recorded between 2 sessions, one week apart [ICC 0.85 (30°/sec) and 0.96 (90°/sec)].

Equipment for testing

Manual testing and the one repetition maximum (1RM)

Manual testing (using the 0-5 Medical Research Council grades) is often used in clinical practice but is insensitive to changes in strength, particularly at

grade three and above [against gravity (Gosselink et al. 2004)]. The 1RM measurement of strength can be used to measure isotonic strength and is a safe and reliable measure of strength in patients with COPD (O'Shea, Taylor, & Paratz 2004). To achieve the maximum, weight should be incrementally increased by one to five kg at intervals of one to five minutes (Gosselink, Troosters, & Decramer 2004). It therefore involves trial and error until the patient is unable to lift any more. Because of the number of repetitions involved in finding the true 1RM, testing can be confounded by fatigue (Chandler et al. 1997). This type of testing may not be suitable in very frail subjects or those with unstable cardiac disease because there are theoretical concerns that increased afterload on the heart during the lifting phase, could worsen left ventricular function. In individuals where there are concerns, the 1RM test can be modified. Estimates of the 1RM can be made from multiple tests, say a 10RM (relative load tests) or multiple RM testing based on target repetitions [goal repetitions per set (Baechle, Earle, & Wathan 2008)].

Cable tensiometers and strain gauges

Cable tensiometers are used to measure isometric strength, and quadriceps strength (QMVC: quadriceps maximum voluntary contraction) has been measured in this way in patients with COPD (Simpson et al.1992). To measure quadriceps strength with a patient in sitting and the knee at a 90°angle; a cable is strapped to the lower leg and connected to the tensiometer (figure 2.4).

Figure 2.4 Subject positioning for measuring QMVC using a seated strain gauge

When the knee is extended, tension is produced in the cable which causes depression of the riser over which the cable runs. This leads to deflection of the pointer on the device and isometric strength is indicated (kg). The tensiometer can measure strength at a variety of joint angles and the equipment is portable (attached to an adapted commode chair on wheels). This portable device was used in the study outlined in appendix 10. The device can also be attached to a software programme which can measure QMVC over a 1 second plateau.

The seated QMVC methodology described was proposed by Edwards in 1977 (Edwards et al. 1977) derived from a healthy population and has been extensively adopted for use in patients with COPD. The coefficient of variation between trials two and three was 2.8% in 62 healthy people.

Dynamometers: mechanical and electronic

Dynamometers measure isometric strength via the application of an external force which either compresses a steel spring (mechanical dynamometer) or moves an electronic force transducer [electronic dynamometer (Gosselink, Troosters, & Decramer 2004)]. HHD can test varying muscle groups by an assessor placing the device over the lever being tested- the device then displays the force produced in kg. Two methods of testing have been described: the 'make'-test and the 'break'-test. In the make-test, the maximal force of the subject is equal to the force of the assessor. In the break-test, the force of the assessor exceeds that of the subject. Higher reproducibility has been found during break-tests (Stratford & Balsor 1994).

The reliability of HHD has been tested in healthy populations (including the elderly) and specific disease groups (Phillips et al. 2000b;Roy and Doherty 2004;Taylor et al. 2004). In 2007, O'Shea and colleagues tested the test re-test reliability of HHD in four muscle groups, in four women and eight men with moderate-severe COPD (O'Shea et al. 2007b). The ICC's were measured to assess the test re-test reliability for individual and group mean scores. Quadriceps ICC was very good with a score of 0.87. Despite this the mean difference between the tests was 2.76 (±7.34 SD) kg and the group 95% CI was -1.91 to 7.42, this increased in individual scores to -13.40 to 18.92. Interestingly the authors commented that a group of patients with COPD would need to have an increase in quadriceps strength of 7.4kg (17%) to be 95% confident that the changes were not just due to variability in the measure. Furthermore the authors advised that HHD may not be suitable to

look at change within an individual, because to overcome the measurement error, strength would need to increase by 10-19kg (34-58%) in the four muscle groups tested. Clearly values of this magnitude may exceed the expected change in these outcomes following a RT programme.

Despite concerns around the within-subject reliability of HHD in patients with COPD it does represent a cheaper alternative to other more expensive modes of isometric testing (cost is approximately £1000), reference values are available (Andrews et al. 1996), it is simple to use and portable.
Hand grip dynamometers measure grip strength and have been used in several studies of patients with COPD. Normative data is available for hand grip strength in several age groups (Mathiowetz et al. 1985) and grip strength is a useful indicator of nutritional status (Vaz et al. 1996).

Isokinetic dynamometry uses a computer-assisted dynamometer (trade names e.g. Cybex® or Kin-Com®) to measure isokinetic and isometric strength of various muscle groups at a variety of joint angles and contraction velocities (Gosselink, Troosters, & Decramer 2004). This device represents the ‘gold standard’ method of measuring strength and both static and dynamic strength were measured in this way for this thesis. The presence of an accommodating resistance in isokinetic testing allows for the safe measuring of torque (Newton metres: Nm) and work (Joules: J) at constant speed throughout the full ROM and therefore gives a comprehensive picture of muscle function. In healthy subjects, a good correlation exists between isometric and isokinetic measurements (Lord et al. 1992) and normal values

are available (Neder et al. 1999). See also section 2.3.1 *Healthy muscle structure, physiology and energy metabolism* which has information on isokinetic normal values for quadriceps strength.

To measure knee extension in sitting, stabilisation of the upper body and thigh can be achieved with straps- see figure 3.2 in *Chapter 3: Materials and Methods*. This is important so that movement at the knee joint is isolated (Weir et al. 1996). The joint centre and axis of rotation of the machine also need to be aligned to produce valid measures (Rothstein et al. 1987). Subjects should be encouraged to make contact with the mechanical end stops during knee extension and flexion. Furthermore, standardised verbal encouragement can be provided throughout the test (Brown & Weir 2001). When combined with additional visual feedback, this is known to increase performance (Campenella et al. 2000).

Whilst highly accurate; isokinetic dynamometry may not be widely available in clinical practice due to its cost (tens of thousands), size and practicality of use (requires training to: calibrate and set up the device, perform the test and to interpret the results).

Electromyography (EMG)

EMG measurements using surface electrodes are an indication of motor unit firing and therefore of the neural component of muscle strength (Broughton 2001). EMG is also frequently used in the assessment of muscle fatigue.

All of these testing methods may be limited by patient effort, learning effect and other extrinsic factors (e.g. arthritis). Peripheral muscle function (namely endurance) can also be measured via non-volitional twitch force; the quadriceps muscle has been investigated in this way. This involves applying supramaximal magnetic stimulation to the intramuscular branches of the femoral nerve to produce a force which is not effort dependant nor subject to learning effect (Swallow et al. 2007a). However this technique may be uncomfortable and technically more difficult to perform than some volitional methods. For these reasons, the technique is generally reserved for research use rather than clinical practice. Using this technique, quadriceps strength has been found to be lower in COPD patents compared to healthy controls and a drop in twitch force after exercise is a useful indicator of muscle fatigue (Saey et al. 2003b).

2.6.2 Whole body and regional muscle mass

Body weight and body mass index (BMI: height normalised body weight) are the easiest and most practical measures of nutritional status. However, changes in weight may be due to changes in fat, muscle or both. These simple measurements may therefore underestimate the prevalence of nutritional depletion because some patients show relative reductions in muscle mass despite being a normal weight (Schols et al. 1991c). For this reason, measurements of body composition are increasingly used for the nutritional assessment of COPD patients. These measurements subdivide the body into a number of compartments. Of importance is the fat free mass (FFM) compartment because this contains functional muscle tissue (Engelen

2000). FFM is calculated as lean mass and BMD. Normal ranges for FFM have not been established, which have led to challenges in defined muscle 'wasting' in individuals with COPD. The FFM index (FFMi) has been proposed as a reference criteria to assess muscle wastage in patients with COPD. This was first described by Baarends and colleagues and body composition was assessed using deuterium and bromide dilution techniques, to measure total body water (TBW) and extracellular water. From these measurements patients were deemed to be wasted if their height normalised FFM was less than 16 kilograms per metres squared (kg/m^2) in men or less than $15kg/m^2$ in women.(Baarends et al. 1997a). These criteria have since been used to define muscle wastage in the COPD population, using bioelectrical impedance as the measurement tool to assess FFM (Mostert et al. 2000;Schols et al. 2005).

A number of direct and indirect measures have been used in the study of (whole-body and regional) muscle mass. Four-site skin-fold anthropometry (SFA) uses callipers to measure the thickness of skin and underlying fat at the biceps, triceps, subscapular and suprailiac areas. SFA may be unreliable in the elderly due to changes in the distribution of fat (Chumlea et al. 1984) and due to extravascular fluid (American Thoracic Society/ European Respiratory Society 1999). An additional problem is that patients with COPD also have increased intramuscular fat compared to healthy controls (Mathur et al. 2007). There are also ways to estimate quadriceps CSA from measures of thigh circumference (Housh et al. 1995) although these measures are based on healthy young men and tend to overestimate in comparison to MRI (Mathur et

al. 2008). Whilst thigh circumference does offer a simple alternative measure in clinical practice, it may not be a sensitive enough measure of muscle mass (Mathur et al. 2008) and assumes that the underlying muscle is circular in shape and that subcutaneous tissue is evenly distributed (Mathur et al. 2008). This may not be the case.

Bioelectrical impedance (BIA) is inexpensive, non-invasive, simple to use and portable; making it ideal for use in clinical practice. It measures FFM based on the differential conduction of an alternating current through body tissue. The information derived is converted to a volume based on the principle that the impedance (resistance) of a conduction system (bodily tissues) is related to its length and cross-sectional area. However it relies on intracellular fluid remaining constant which it may not in the elderly or those with a chronic disease. Furthermore, BIA may not be sensitive enough to detect changes in mass in response to interventions [e.g. RT (Nelson et al. 1996;Sipila & Suominen 1995)].

U/S can be used to measure the CSA and thickness of superficial muscles via the reflection of high-frequency sound waves from the tissues. U/S is easy to perform as the equipment is portable. Rectus femoris CSA, as measured by U/S, has recently been found to correlate well with strength (Seymour et al. 2009) and work at our own institution has shown that U/S is sensitive to changes in mass in response to RT (Menon et al. 2009) in patients with COPD. The change in quadriceps CSA after RT was significantly greater

when measured by U/S [21.1 (16.4) %] as compared to DEXA [6.4 (3.0) %], in this study (p=0.002).

CT and MRI are the 'gold standard' tools to measure muscle mass. They can measure the volume and CSA of individual muscles (e.g. the vastus lateralis) as well as muscle groups [e.g. the quadriceps (Mathur et al. 2008)]. Reduced quadriceps CSA has been detected in patients with COPD compared to healthy controls using these methods and CSA is closely correlated with volume [r= .61 to 0.94 for both groups (Mathur et al. 2008;Vilaro et al. 2009)]. These correlations were equally strong at three specified levels of the thigh (30, 50 and 80% of the thigh length). CT and MRI have also been used to detect an increase in strength in response to training in patients with COPD (Bernard et al. 1999;Kongsgaard et al. 2004). However these radiological techniques are expensive and require access to cumbersome equipment with trained technicians (Ross 2003a). Furthermore CT involves exposure to ionising radiation which is not ideal for serial measures (Mathur et al. 2008). To reduce this time and risk, often a single slice is used as an indicator for the entire muscle (Mathur et al. 2008).

DEXA (figure 2.5) is an attractive alternative to CT and MRI, has been validated against deuterium dilution (a measure of total body water from urine or saliva samples) in patients with COPD (Engelen et al. 1998) and has been shown to correlate well with CT (Wang et al. 1996). DEXA measures BMD, bone-free lean/ FFM and fat mass via two low-energy x-ray beams which involve minimal radiation exposure. The scan takes less than 10 minutes to

complete and regional analysis can be performed (Menon & Steiner 2009). Importantly, changes in hydration do not appear to affect the accuracy of the measurements (Kohrt 1995). However, the DEXA equipment is expensive, large and may not be routinely available in clinical practice. Furthermore, whilst DEXA can determine regional mass (e.g. of the thigh); it can not differentiate between individual muscles. Thigh and whole-body FFM were measured using DEXA for this thesis.

Figure 2.5 DEXA scanner

Measures of FFM in COPD patients have been compared using DEXA, SFA and BIA prior to the start of PR (Steiner et al. 2002). Relative to DEXA, FFM was overestimated by SFA and underestimated by BIA. The prevalence of nutritional depletion detected by DEXA, BIA and SFA was 49, 48 and 38% respectively. These between-method differences highlight that the tools to calculate FFM can not be used interchangeably (Steiner et al. 2002).

2.6.3 Physical Activity (PA)

PA is defined as, ‘any bodily movement produced by skeletal muscles that requires energy expenditure and produces progressive health benefits’ (Anon 1996). This definition is different to exercise which involves planned bodily movements that are repetitively performed to improve or maintain fitness (Caspersen et al. 1985). The health benefits of maintaining PA in healthy people are well documented. However it is only in recent years that we have realised the importance of PA in patients with COPD. It may be that part of the deconditioning associated with COPD is due to inactivity (Morgan 2008). Levels of PA are reduced in patients with COPD, when compared to healthy age-matched subjects (Pitta et al. 2005). This is the case even in those with mild disease. PA levels are also known to decrease in the days before and during an AE and PA levels are not regained, even at 3-months post-AE (Pitta et al. 2006a). Reduced PA in patients with COPD is associated with a poorer prognosis (increased time to death) and an increased risk of hospitalisation (Garcia-Aymerich et al. 2006a;Pitta et al. 2006a).

One of the aims of PR is to improve physical functioning (Hunter et al. 2006). To change domestic PA requires a behaviour change and a commitment to being more physically active (Morgan 2008). The objective monitoring of PA in COPD is therefore now of clinical interest particularly when we aim to measure changes in PA in response to rehabilitation programmes or other interventions. Quantifying daily PA measures a different construct to functional capacity (i.e. a maximal exercise test). Functional capacity relates to what level of performance subjects are capable of achieving. When we measure PA

we are observing what patients choose to do (Leidy 1994). It is important to differentiate between these dimensions when assessing patients with COPD, as habitual PA appears to have a protective benefit. We know that PA is only marginally correlated with the degree of airflow obstruction in this population, indicating that other factors are involved, such as peripheral muscle weakness (Garcia-Aymerich et al. 2006).

The outcomes of interest related to PA are: step count, energy expenditure (EE) and metabolic equivalents (METS), amongst others. EE is the amount of energy (calories) that a person uses to breathe, circulate blood, digest food and be physically active (Davies 2007). METS are a multiple of the resting rate of oxygen consumption per minute. One MET is equal to that of the oxygen consumption at rest, which is approximately 3.5mls of oxygen/kg/min or one kcal of oxygen/kg/hour. Three METS would correspond to brisk walking (Ainsworth et al. 2000). The 'gold standard' method of measuring PA is by direct observation (Sirard & Pate 2001). However this method is impractical and hugely labour-intensive. EE can also be accurately assessed used laboratory-based doubly labelled water (DLW) or indirect calorimetry techniques. These techniques are costly, confined to the laboratory and require skill to conduct the tests/ analyse the results. Furthermore, they are unable to characterise PA patterns as they only give total energy expenditure over a period of time (Sirard & Pate 2001).

Traditionally, PA has been derived from questionnaires, interviews, heart rate (HR) monitors or motion sensors (Agusti 2008;Pitta et al. 2006b), as these are

more practical measures of PA and have often been validated against some of the ‘gold standard’ measures of energy expenditure described above. Questionnaires or interviews are a simple and inexpensive way to measure PA. However, these subjective measures are open to inaccuracy and bias in recall (Pitta et al. 2006b). This is a particular problem in very sedentary patients when seemingly small changes in PA may confer large gains in function or health status (Morgan 2008). It has been suggested that questionnaires may be useful to compare groups of patients but lack the sensitivity to detect changes within an individual (Pitta et al. 2006b).

PA was measured in this thesis using the adapted PA questionnaire for the elderly [(Voorrips et al. 1991) appendix 14]. This questionnaire was chosen as it is not disease-specific and could therefore be used to assess both patients and healthy elderly controls. The questionnaire consists of scores in household activities, sporting activities and leisure activities to produce an overall activity score of 0-35. The questionnaire is interviewer-led and asks about activities within the last year; a higher score indicates a greater level of PA. The researcher is responsible for giving an intensity code for each of the sporting and leisure activities. This code is based on the energetic costs of activities [originally based on the activity questionnaire described by Baecke and co-workers (Baecke et al. 1982)]. Test-retest reliability, and validity of the modified questionnaire, compared to two independent methods of assessing PA (pedometer and 24hour activity recall) in the elderly have been established (Voorrips et al. 1991). The questionnaire has been used to describe COPD populations [e.g. in relation to muscle weakness or compared

to healthy controls (Engelen et al. 2000;Serres et al. 1998)], rather than as an outcome measure of PR. In the study by Serres and co-workers, PA using this questionnaire was found to be significantly lower in patients (5±1) compared to healthy controls (10±2, for the total score. $p<0.05$). Furthermore, low PA was associated with poor muscular endurance [$r=0.60$, $p<0.05$ (Serres et al. 1998)].

The Duke Activity Status Index (DASI) was another self-administered questionnaire used in this thesis. The DASI (Hlatky et al. 1989) was developed in a cardiac population and has good correlation with peak oxygen uptake (spearman's correlation coefficient r= 0.80 in n= 50). Its utility and relationship to oxygen uptake in patients with COPD is unknown. The DASI is a simple, 12-item instrument that provides a patient's self-assessment of their functional abilities. The DASI was validated to estimate maximal oxygen consumption (VO_2 peak) measurements at peak exercise (Hlatky et al. 1989). METs can then be calculated by dividing the estimated VO_2 peak by 3.5 (as one MET is equal to that of the oxygen consumption at rest, which is approximately 3.5mls of oxygen/ kg/ min). DASI scores range from 0, which represents an inability to carry out any of the listed activities, to 58.2, which represents the ability to carry out all of listed activities.

To combat the inadequacies of questionnaires, many devices are now available which can measure PA more accurately (Agusti 2008;Steele et al. 2003). These devices are either pedometers (step counters) or accelerometers [detect quantity and intensity of movement (Agusti

2008;Steele et al. 2003)]. Pedometers are simple, inexpensive devices which measure movements in a vertical plane, i.e-steps. They are widely available to the general population, easy to use and provide subject feedback. One frequently used pedometer; the Yamax digi-walker CW-700 (Yamax corporation, Tokyo, Japan), costs around £20. Validation against visual counts is generally good (in healthy adults) but they may underestimate walking at slower speeds (Cyarto et al. 2004;Tudor-Locke et al. 2002). Also in healthy volunteers, accuracy in the step count recorded (pedometer Vs visual counts), improves at faster walking speeds (Turner et al. 2010) This may be a problem in sedentary COPD patients who walk at slower speeds as the underestimation of steps, due to lack of sensitivity, may be de-motivating. Also pedometers do not detect other forms of movement in different directional planes, the intensity of activity or time spent doing alternative activities to walking (Pitta et al. 2006b). Despite these limitations, step counts have become a popular outcome measure. The majority of the general population are familiar with the public health campaign to encourage adults to reach their recommended 10,000 steps per day. Less than 5,000 steps per day is deemed ‘sedentary’ (Tudor-Locke & Bassett, Jr. 2004).

Accelerometers are preferred, as they can quantify movement and its intensity (Steele et al. 2003). Accelerometers measure acceleration created by bodily movement which are converted to counts. More sophisticated devices can also measure the time spent doing mild, moderate and vigorous activity (in terms of METs) and can estimate energy expenditure (e.g. the DynaPort

Minimod® by McRoberts, Hague, Netherlands and the Sensewear® armband by Bodymedia, Pittsburgh, USA - figure 2.6).

Figure 2.6 Sensewear® activity monitor- position on subject's arm

Most modern accelerometers are multiaxial and are therefore able to detect movement in more than one bodily plane. Accelerometers can store data for long periods of time (Pitta et al. 2006b). It is generally agreed that two days of recording is the minimum required for accelerometers; ideally three to five days of 12 waking hours achieves reliability for adults (Trost et al. 2005). Days should be standardised (i.e. weekdays/ weekends) as activity may differ. This is especially true of those who are working. The number of days that an accelerometer can record data varies between devices and is determined by battery life and storage capacity (Davies 2007). Computer software is required to view and analyse the data.

The disadvantages with accelerometers are the relatively expensive cost (including computer software) when compared to questionnaires, technical

issues (e.g. battery level) and sensitivity to external vibrations (e.g. from being in a vehicle) (Patterson et al. 1993;Pitta et al. 2005;Pitta et al. 2006b).

The ActiTrac® activity monitors, used in this thesis, [IM Systems, Baltimore (MD) USA] are bi-axial accelerometers. These monitors are simple to use for patients, with no on/off power buttons. The ActiTrac® software is also uncomplicated for clinicians who use it to initialise the monitors and download the data. Graphs can be displayed to view activity patterns over the day. These monitors were chosen to assess PA in this thesis because they were available for use at the time of the study and are also relatively inexpensive (approximate cost: device £400, software £230); particularly in comparison to other devices on the market (Approximate costs: DynaPort Minimod device= £830, Sensewear Armband device= £660, software= £1000). The ActriTrac® has been used to measure activity in healthy individuals and is a valid way of measuring energy expenditure under controlled conditions [as compared to indirect calorimetry (Welk et al. 2003)]. The correlation coefficients between measured and predicted EE for the ActiTrac® were r=0.94 (Welk, Almeida, & Morss 2003). Prior to their use in patients with COPD, it was important to examine whether or not the devices could detect the slow speeds of walking typically employed by patients. Therefore, the devices were tested at 3 speeds of walking (slow, moderate and fast) in a healthy individual (the author of this thesis). More details regarding this activity monitor and testing prior to use in patients are provided in chapter 7. Unfortunately, the device does not measure steps or energy expenditure and the output may not therefore be clinically meaningful for patients or clinicians.

Accelerometers and pedometers have been used in patients with COPD as an outcome measure of PR (Pitta et al. 2008), and these have been summarised in a review by Troosters last year (Troosters et al. 2010). In the nine studies assessed, there was huge variation in the improvement in PA seen after PR compared to baseline. This probably reflects heterogeneity in the PR programmes and devices used to collect PA data. The percentage change in PA after rehabilitation ranged from 0 (Steele et al. 2008) to 70 % (de Blok et al. 2006). This review highlights that changes in PA after PR are not guaranteed. Furthermore, we don't know what a clinically relevant improvement in PA after PR would be and this is likely to differ between patients and patient groups.

Simple activity monitors and pedometers can also be used as a training aid or to monitor exercise compliance (Hunter et al. 2006) if the devices provide patient feedback. One study by deBlok (de Blok et al. 2006) used a pedometer to provide feedback to patients about their walking during a PR programme and gave PA counselling advice. A control group received only conventional PR. For the group that had the pedometer, steps increased by 1430 per day (or 69%) from baseline compared to controls that had an increase of 455 steps (or 19%). However no other secondary outcome measures improved in this study and patients in the experimental group achieved a step count after PR that still fell short of the 10,000 per day public health campaign [steps=3512 (95% CI 1797-5227)].

2.6.4 Whole-body Exercise Performance

Reduced exercise capacity is a well documented feature of COPD and limiting factors may vary and change over time (Saey & Maltais 2005). Ventilatory limitation (including dynamic hyperinflation and reduced oxidative capacity), abnormal gaseous exchange, cardiovascular limitation, skeletal muscle dysfunction and psychosocial problems have all been identified as factors which can influence exercise capacity (Gallagher 1994;Saey & Maltais 2005). It has been debated which of these are the primary causes (Aliverti and Macklem 2008a;O'Donnell & Webb 2008), however it seems reasonable that as the disease progresses that more of these factors will play a role in exercise limitation (Aliverti & Macklem 2008b). These factors can be measured in the context of a whole-body exercise test and a number of objective methods have been developed to assess exercise tolerance in patients with COPD.

Generally it is lower-limb exercise capacity which is measured. The information gathered from these tests can also be used to determine the need for PR, surgery, a walking aid or AOT; prescribe an exercise programme and also to measure the response to treatment (Johnson 2004).

Laboratory-based exercise tests

The ‘gold standard’ measure of maximal exercise capacity is the laboratory-based cardiopulmonary exercise testing [CPET (Palange et al. 2007)]. Cycle ergometry or treadmill tests are the most commonly employed. These tests are usually incremental in nature (Ross 2003b). During cycle ergometry the individual is

usually instructed to cycle at a constant speed [often around 50 revolutions per minute (RPM) is sustainable] and after one minute periods, the work rate is increased by a specified number of Watts per minute (W/min). This is continued until the individual is no longer able to maintain the set speed or is limited by symptoms. Treadmill tests are broadly similar in so far that the individual is required to walk at a designated speed; the gradient then increases to represent an increased work load (Singh et al. 1994). These tests also allow the individual to be monitored closely for vital signs and observations of exercise limitation, such as ventilatory, cardiac or leg fatigue. For individuals who have COPD, peak oxygen uptake (VO_2peak) is a measurement which is frequently focused upon (Palange et al. 2007). This is an indication of maximal exercise capacity and is defined as the highest value of oxygen uptake that is attained during an incremental exercise test. Work rate is also recorded, commonly reported in Watts (W). In a meta-analysis of 13 trials of cycle ergometry [(Lacasse et al. 2006) 268 participants and 243 controls], the common effect size was 8.4 W [95% confidence interval (CI) 3.4-13.4] following PR. This equated to an 18% improvement in peak work rate from baseline in a similar review (Troosters et al. 2005). The minimal clinical important difference (MCID) for a change in W after intervention has been reported. The MCID represents the minimum by which the subjects improve to notice a difference. Data from the NETT trial suggests an MCID of 4W following pre-LVRS rehabilitation (Puhan et al. 2011).

Field exercise testing

Whilst laboratory-based exercise tests are the gold standard, they may be impractical in clinical practice. Field tests are therefore often employed as an

alternative. The most common field tests are the six minute walk test [6MWT (Anon 2002)] and the incremental shuttle walking test [ISWT (Singh et al. 1992)].

According to the ATS Guidelines (2002), during the 6MWT the individual is instructed to walk as far as possible during six minutes around a 30 metre (m) course which is designated by two cones, and marked out at three m intervals. The individual is permitted to slow down, stop and rest as necessary. The operator is required to track the distance covered by the individual during the test. A practice walk is not required, but should be considered. It is important to standardise the test course and conduct because it is known that encouragement and course layout may influence the outcome.

The ISWT (Singh et al. 1992) is an externally paced field test (figure 2.7). The individual is provided with standardised instructions prior to commencing the test. They are then required to walk around a ten metre course along a flat surface, which is demarked by two cones placed nine metres apart, allowing 0.5 m at each end for turning. The speed of walking is dictated by an audio signal which begins slowly, and increases at one minute intervals. The test is continued until the individual is too breathless or fatigued to continue, or can no longer maintain the walking pace. A practice walk is required as there may be a significant learning effect with repeat testing (Singh et al. 1992). A ‘true’ test should be performed after a 30 minute rest. VO_2 peak during the ISWT correlates favourably with oxygen consumption during standard treadmill tests (Singh et al. 1994) and during the test a linear response in lung gas exchange indices occurs (Onorati et al. 2003). This

test is therefore useful for measuring the distance walked to predict maximal oxygen uptake.

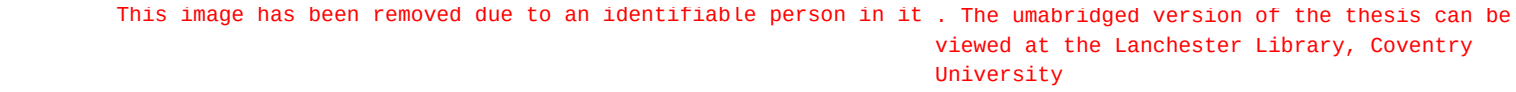


Figure 2.7 ISWT in practice

The response to the 6MWT and the ISWT has been compared (Luxton et al. 2008). The physiological response to the ISWT is gradual and mirrors the response observed in an incremental cycle test. This is not seen in the 6MWT where a peak response is observed within the first three minutes.

It is currently accepted that a change of around 48m for the ISWT (Singh et al. 2008) and 54m (Redelmeier et al. 1997) for the 6MWT represent the MCID for these outcomes

2.7 Summary

Quadriceps muscle dysfunction is a key cause of exercise intolerance in patients with COPD, manifested by reduced muscle mass and strength. This problem also imposes a burden to the health system as quadriceps dysfunction is an independent predictor of hospitalisation and mortality. Importantly, the quadriceps may provide a target for therapy in an otherwise irreversible lung disease and changes in strength after RT are well known.

Dietary protein has been shown to induce protein synthesis in healthy young adults. However there is an impaired response in healthy elderly subjects and merely providing dietary protein may not be effective in increasing protein synthesis. It may be that an anabolic stimulus, such as exercise is needed. The timing of supplementation in relation to RT may also be an important factor in the response for older people.

This thesis describes a RCT which aims to explore the role of protein supplementation given immediately after RT, upon functional outcomes, in patients with COPD. Secondary aims were to precisely explore the training intensity progression, fatigue profile and cardio-respiratory load imposed by the RT and to examine the measurement properties of the ActiTrac® accelerometers.

Chapter 3

Materials and Methods

3.1 Introduction

This chapter will describe all methods employed in chapters 4-6. These chapters explore the main components of the randomised controlled trial discussed in this thesis. This includes: the main study outcomes (chapter 4), the profile of the RT programme (chapter 5) and the cardio-respiratory load of the training (chapter 6). The methodology for the reliability and sensitivity of the activity monitors is described in detail in chapter 7 and is therefore not discussed comprehensively here. This chapter will examine the study design, recruitment of subjects and outline the interventions compared in this thesis. It will also comprehensively describe the outcome measures and the methods of statistical analyses employed in this thesis.

3.2 Ethical approval

The study described in this thesis received ethical approval from the Leicestershire, Northamptonshire and Rutland Research Ethics Committee 1 (Reference: 06/Q2501/138), Leicester City Primary Care Trust (Reference: 0696) and was sponsored by the University Hospitals of Leicester (UHL) NHS Trust (Reference: 10146). Funding was provided by a Medical Research Council experimental medicine grant and the study was registered with the International Standard Randomised Controlled Trial Number Register (Reference ISRCTN22764439). Recruitment took place between January 2007 and January 2010.

Subjects were provided with written information and given at least 48 hours to consider the information and ask any questions. Patient information leaflets for COPD patients and healthy controls are shown in appendices 3 and 4. All subjects provided written informed consent (appendix 5) prior to participation in the study. Consent was taken by myself or Dr Menon. It was made clear that refusal to take part or withdrawal from the study would not affect any future care. The GP of the subjects were informed that their patient was involved in the study and were provided with an information leaflet outlining the study. A copy of the consent form and patient information sheet were filed in the subjects' medical notes. New notes were created for any subject who was not previously known to UHL NHS Trust.

All assessments and interventions described in this thesis took place in the exercise laboratory and respiratory physiology department at Glenfield Hospital which is part of the UHL NHS Trust.

3.3 Study design

The study design was a double-blind, randomised placebo-controlled trial of protein supplementation throughout a RT programme. The study objectives were met by comparing skeletal muscle function, muscle mass and PA at baseline, during and after a standardised 8-week RT programme in patients with COPD and age-matched healthy controls. COPD patients were also randomised to receive a nutritional supplement or a non-caloric placebo during the course of the RT programme. Patients were stratified prior to randomisation to ensure that equal numbers of wasted and non-wasted

patients were recruited to each arm of the study. Patients were deemed to be wasted if their height normalised fat-free mass (FFM) was less than 16 kg/m^2 in men or less than 15kg/m^2 in women from DEXA analysis (see section 3.8). The study design is summarised in figure 3.1.

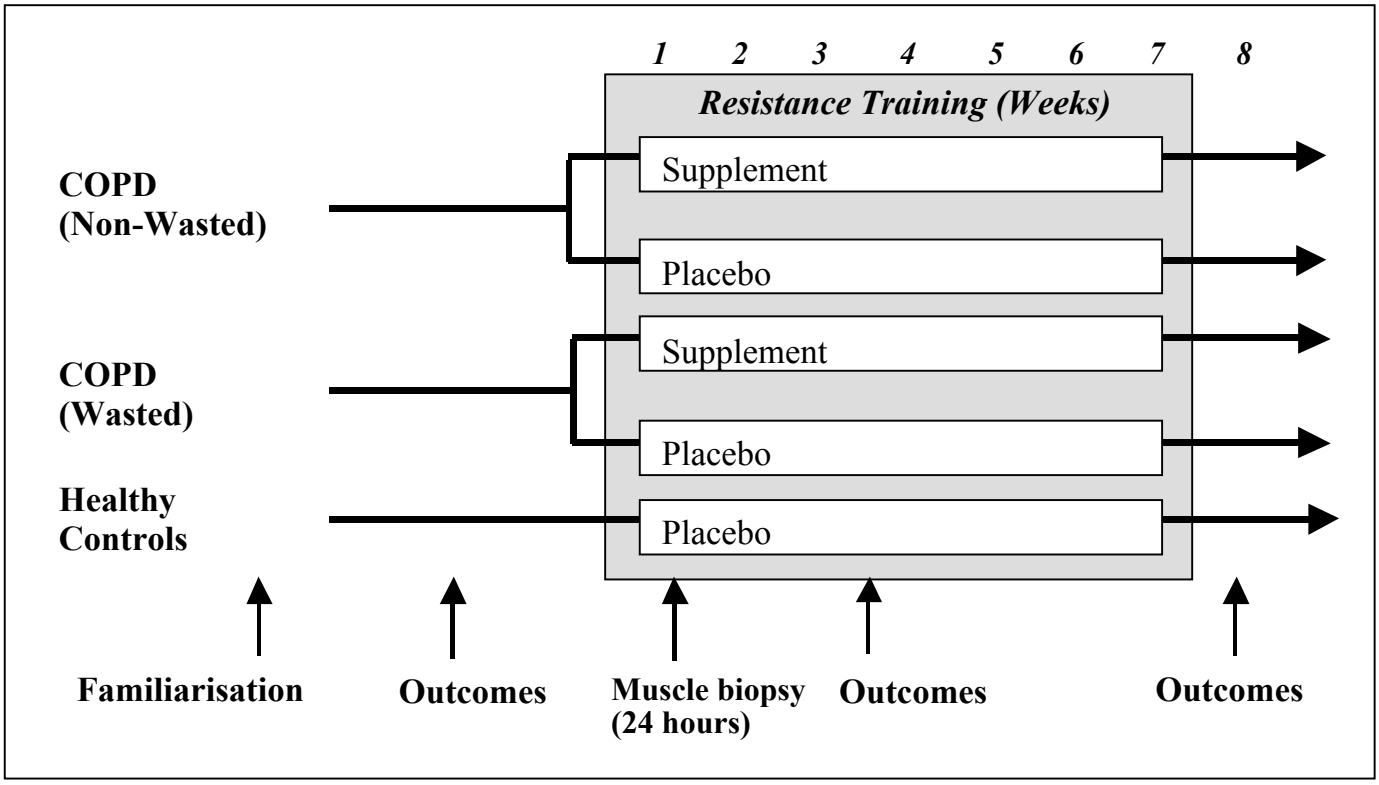


Figure 3.1 Study Design

3.4 Randomisation and blinding

A third party randomisation service was provided by the University of Nottingham Clinical Trials Unit (CTU). This facility was internet based and involved logging onto the system prior to the subjects' first training session. The following subject details were entered: sex, date of birth, study number and whether they were wasted/ non-wasted from DEXA analysis. Randomisation occurred in varying blocks of the following sizes: 2, 4 and 6.

The system then provided a randomisation number which matched the treatment label on the supplement boxes. A person independent of the study (Dr Louise Sewell) received the treatment allocation list at Glenfield Hospital and labelled the treatment boxes accordingly. This enabled double blinding (subject and researcher).

Importantly, the system was set up to stratify subjects based on their gender and whether they were wasted/ non-wasted from DEXA analysis. Healthy subjects were not randomised and received a box of placebo sachets for the duration of the study.

3.5 Recruitment sources, inclusion and exclusion criteria

Subjects with COPD were recruited from respiratory out-patient clinics at Glenfield Hospital, from local GP practices and from the respiratory specialist nurses working in the community. Invitation letters were also sent to those who had been referred for PR at Glenfield Hospital and to PR graduates who had completed their treatment at least one year ago. For those subjects who had been referred for PR, they were able to complete the study whilst remaining on the waiting list and went onto start PR as planned. As the study interventions in this thesis did not constitute comprehensive PR, we also offered a place in PR to those who felt that this was needed after completion of the study. In accordance with ethical standards, subjects only participated in one research study at any one time. Motivated patients, prepared to exercise thrice weekly were recruited. This may have introduced selection bias.

Inclusion criteria: COPD subjects

Subjects were enrolled who had moderate to severe airflow obstruction on spirometry [GOLD stages II-IV (FEV_1/ FVC ratio <70%), a diagnosis of COPD and a significant reduction in exercise tolerance (MRC grades III-V). Patients were clinically stable (no exacerbation in the previous 4-weeks) and able to carry out lower-limb RT.

Exclusion criteria: COPD subjects

Exclusion criteria were oral corticosteroid, anticoagulant and long-term oxygen therapy as well as type I and type II diabetes. These criteria were all due to potential problems in either the muscle biopsy procedure or analysis (vastus lateralis biopsies were taken as part of the wider study by Dr Menon). These criteria therefore excluded the most severe patients and may reduce the external validity of the findings. Those with co-morbid conditions preventing exercise training, such as lower-limb arthritis, were also excluded. Furthermore, PR graduates were asked to wait at least a year after completing the programme before starting the study; because the benefits of rehabilitation have been shown to persist for at least 12-months (Griffiths et al. 2000;Ries et al. 2007).

Recruitment of healthy subjects

Age-matched healthy controls were recruited from the local population via advertisements including posters, bulletins on the UHL NHS Trust intranet and visits to the annual UHL NHS Trust open day. Furthermore, a number of

patients' spouses enrolled. This may have introduced selection bias as they would have a vested interest in the results of the study.

Inclusion Criteria: Healthy Subjects

Healthy subjects who had no evidence of airflow obstruction on spirometry (FEV_1 > 80% predicted) and were able to carry out lower-limb RT were included. A sedentary healthy cohort were required to provide comparison with the COPD group and therefore healthy subjects did not participate in regular exercise (defined as ≥ three exercise sessions per week).

Exclusion Criteria: Healthy Subjects

Exclusion criteria were the same as for the COPD subjects. In addition, healthy subjects who met the criteria for FFM depletion were also excluded.

3.6 Interventions

Quadriceps resistance training

The RT programme lasted for eight weeks and comprised of three supervised thirty-minute sessions per week. Supervision was provided by a trained Physiotherapist (LH- author) who gave standardised instructions and all subjects could visualise their performance on the screen at all times. Training took place using an isokinetic dynamometer (Cybex II Norm: CSMi, Stoughton, USA).

Positioning and stabilisation of the subject were standardised according to manufacturer guidelines. This involved the subjects sitting upright in a seated position. The chair monorail and back translation were adjusted so that the centre of the dynamometer head was in line with the subjects' knee joint line. A seatbelt, thigh strap and contra-lateral limb stabiliser were used to ensure that movement of other body parts was limited. In addition, subjects were asked to fold their arms (see figure 3.2). The knee/ hip adaptor pad was then strapped to the distal part of the tibia at a level which was approximately five centimetres above the lateral maleoulus of the ankle (see figure 3.3).

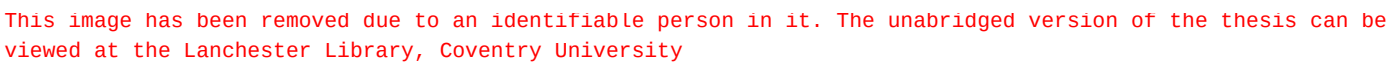


Figure 3.2 Isokinetic dynamometer subject position

The subjects' leg was held out so that the knee was straight (0 degrees) and range of movement was set between 10-80° flexion. The weight of the limb

was then measured to allow the computer system to correct for gravity in its calculations (Chan et al. 1996).

Subjects then performed five sets of thirty maximal knee extensions, moving the knee/ hip adaptor bar up and down. The contractions were isokinetic and concentric at a PAV of 180°/sec. Each set was separated by a minutes rest and both legs were trained. The work of the knee flexors to move the leg back to the resting position is not presented because patients were not asked to forcefully pull back. Additionally, subjects also received one minute of continuous passive movement (flexion/ extension) before and after the training to act as a warm-up/ cool-down. This RT protocol was known to restore muscle mass, post-immobilisation in healthy young men (Jones, Hill, Krasney, O'Conner, Peirce, & Greenhaff 2004) and was found to be tolerable by frail COPD patients in a pilot study (Williams, Flora, Sandland, Singh, & Steiner 2007).

Figure 3.3 Positioning of knee/ hip adaptor

The basic measurements recorded were the peak torque (Newton-metres: Nm) and total work done (Joules: J) for each of the five sets. The highest value for each leg was also documented (see recording log, appendix 6).

Patients were withdrawn from training if they had a disease exacerbation meaning that they were unable to attend a training session for ≥ 10 days or if they complained of continued musculoskeletal pain.

Nutritional supplementation

COPD patients were randomly assigned to receive either a dietary protein supplement or a placebo after training throughout the study period. Healthy volunteers received the placebo only. The supplement contained 19 grams (g) of protein and some carbohydrate (Vitargo Gainers Gold: Swecarb, Sweden) and was mixed with up to 500 millilitres (mls) of cold water. The protein-carbohydrate mix was deemed sufficient to saturate post-exercise muscle protein synthesis and to ensure insulin availability, above the level known to inhibit muscle protein breakdown in healthy young volunteers (Rennie 2007). The placebo was an identical volume, non-nutritive and non-caloric drink. The supplement and placebo looked identical both in powder form and once mixed with water. The only difference was that the supplement was heavier (by 45 g). For this reason, the sachets or boxes weren't handled by researchers. The full ingredients of both the supplement and placebo are shown in appendices 7A and B.

Supplementation took place immediately after each training session, as the timing of protein intake appears to be critical (Esmarck et al. 2001). All subjects were responsible for making their own drinks from the sachets in their allocated box. This ensured that the boxes weren't handled by the study personnel and therefore blinding remained in tact. However subjects were supervised to ensure that drinks were taken in full prior to leaving the exercise laboratory.

3.7 Measurement of symptoms during resistance training

Breath-by breath analysis

Breath-by-breath measurements of gas exchange and ventilation were taken in a subset of subjects during one RT session; to determine the load on the cardio-respiratory system. This is described in detail in chapter 6.

Measurement of breathlessness

Perception of breathless was measured before and after each RT session using the Modified Borg scale [(Borg 1982) appendix 8]. This is a categorical scale with ratio qualities and is sensitive to changes in respiratory effort (Jones et al. 1985). The scale ranges from 0 ("no breathlessness") to 10 ("the worst breathlessness you have ever experienced").

Measurement of perceived exertion

Rates of perceived exertion (RPE) were measured before and after RT using the modified Borg scale [(Borg 1982)- appendix 9]. The scale ranges from 6

(“no exertion”) to 20 (“maximal exertion”). The scale takes into account breathlessness and muscle fatigue to give an overall score.

Other physiological measures

Continuous monitoring of SpO_2 and HR were measured throughout each RT session using a portable pulse oximeter with finger probe (PULSOX-3: Konica Minolta, Osaka, Japan). Resting and post-exercise values were documented.

3.8 Outcome measures

Outcomes were assessed before and after the 8-week RT programme. Of note, subjects were familiarised to all tests prior to the baseline assessment to prevent a learning effect. The need for one practice isometric and isokinetic strength test, prior to baseline testing, is apparent from the data presented in appendices 10 and 11. Muscle strength and muscle mass were also assessed at 4-weeks (mid-point, prior to training sessions 12-14). These 4-week, interim results are presented in chapter 5 only when considering the how RT intensity relates to functional outcomes. The results at 4-weeks are not presented in chapter 4. Muscle biopsies of the vastus lateralis and blood tests were taken immediately prior to the first RT session, 24-hours after the first RT session, at 4-weeks and at the end of 8-weeks by Dr Manoj Menon to explore the molecular mechanisms underpinning muscle growth (not discussed in this thesis).

An outline of the study visits is shown in figure 3.4.

Visit	Consent	Practice exercise tests	Lung function tests	Muscle biopsy	Blood test	DEXA	Muscle strength	Cycle ergometry	Activity monitors and questionnaires	Resistance training
1: Familiarisation	x	x	x							
2: Baseline						x	x	x	x	
3: Training session 1				x	x					x
4: 24 Hours				x	x					
Training week 1-4										x
5: Mid Point				x	x	x	x			x
Training week 5-8										x
6: Post study				x	x	x	x	x	x	
7: 6 Months							x			

Figure 3.4 Study visit schedule

Clerking information

During the first visit**,** general clerking information was collected. e.g. demographics, medical history, medication list, smoking history and social information. In addition, height was measured in cm (to the nearest 0.1cm) using a wall mounted measuring stick and weight measured in kg (to the nearest 0.1kg) was measured using floor scales (both SECA: Hamburg, Germany), to calculate BMI.

Assessment of quadriceps strength

Both isometric and isokinetic strength of the dominant quadriceps was measured using an isokinetic dynamometer (Cybex II Norm: CSMi, Stoughton, USA). The same standardised positioning of the subject was used as for the RT (figure 3.2). Peak isometric strength (Nm) was measured during six attempts at a maximum static contraction, with the knee fixed at 70° flexion. As part of a methods comparison, the same procedure was also carried out on a seated strain gauge and with a HHD in a sub-group of participants (see appendix 10). The test re-test reliability of the more affordable, portable methods were compared to the gold standard cybex measure. HHD was the least reliable. Both the cybex and strain gauge had ICC values of 0.90 and above.

Isokinetic strength was also assessed during two sets of five knee extensions at an angular speed of 60°/sec. The highest peak torque (Nm) and total work done (J) for the best set was recorded. Furthermore, isokinetic peak torque (Nm) and total work done (J) on each leg was averaged over weeks 1-8 of

training to produce 180°/sec results (reported in chapter 5). Resting and peak measures of SpO_2, HR, Borg breathlessness levels and Borg RPE levels were taken in the same way as they were for the RT.

Assessment of total body and regional muscle Mass

Total body and thigh FFM were measured using DEXA (Lunar Prodigy: GE Healthcare, Chalfont St. Giles, UK). Subjects were asked to lie flat on the DEXA table within the boxed area for the duration of the scan (approximately five minutes). Straps were placed around the knees and ankles to hold them in position. See positioning diagram (figure 3.5). Metallic items were removed from the body prior to the scan.

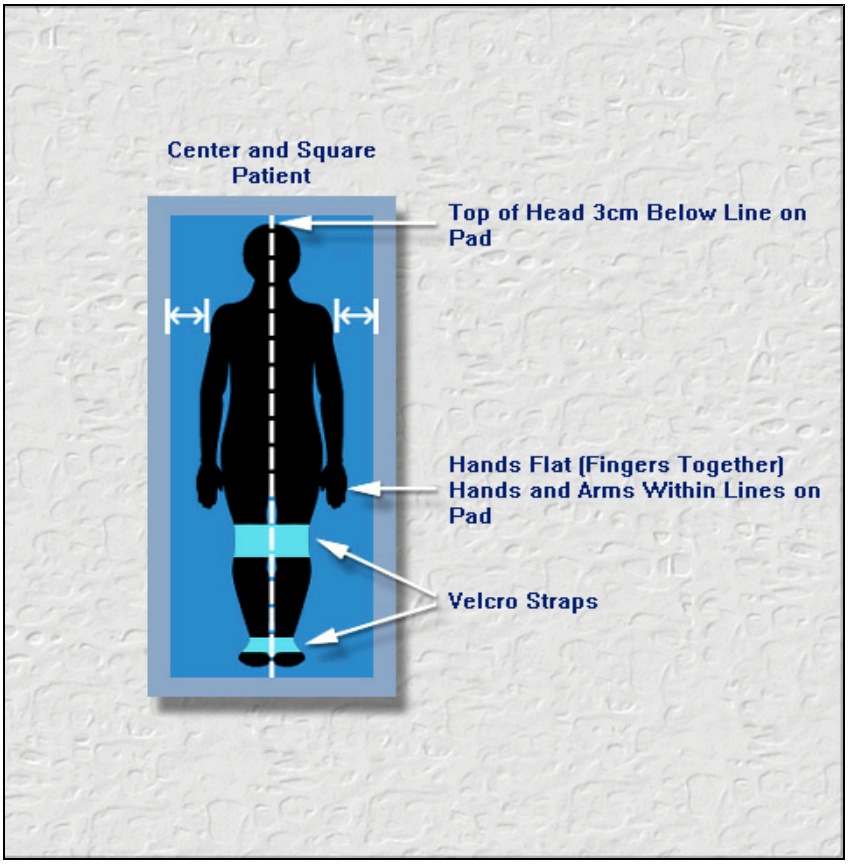


Figure 3.5 DEXA subject positioning

FFM (g) was calculated as lean mass + bone mineral mass. To determine the lean mass of the dominant thigh, a region of interest (ROI) was traced using custom analysis. The upper limit of this ROI was the lowest point of the ischial tuberosity. The lower limit was the knee joint line. The pubic symphysis and the most lateral part of the thigh were used as the medial and lateral limits [(Delmonico et al. 2008) see figure 3.6]. The total body FFM was also expressed as an index (FFMi: lean mass + bone mineral mass/ height). Subjects were deemed to have FFM depletion if their height normalised FFM index was below 16kg/m^2 for men and below 15kg/m^2 for women. As DEXA is primarily used in the screening of osteoporosis; subjects' GPs were informed if osteoporosis or osteopenia were apparent.

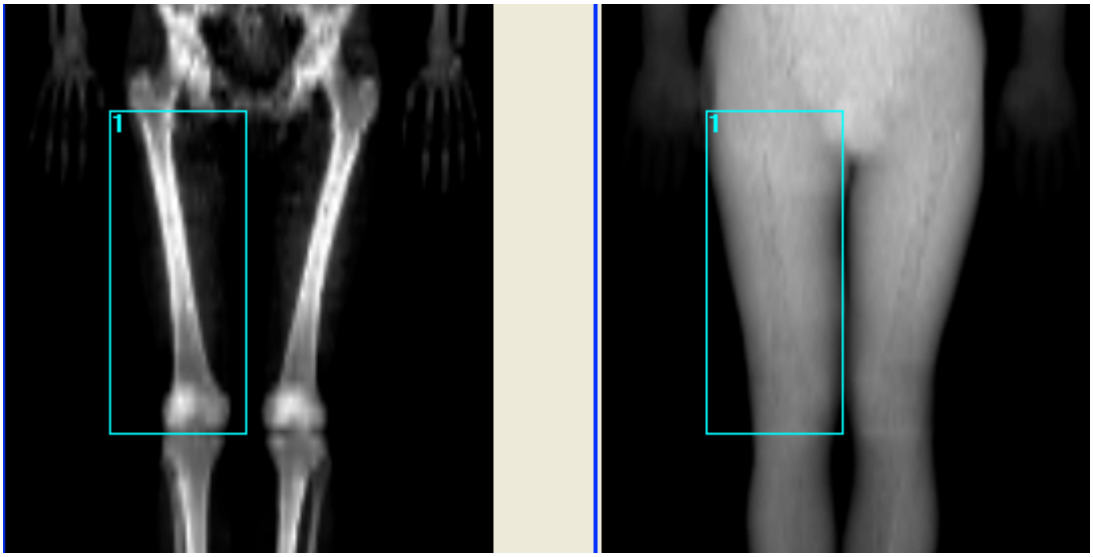


Figure 3.6 Thigh FFM ROI

Assessment of physical activity

PA was measured in a subgroup of participants using two, none disease-specific questionnaires (Voorips and DASI) and the ActiTrac® activity monitor.

The Voorips questionnaire was performed at baseline only. The DASI and the 7-day activity monitor results were analysed before and after the 8-week RT programme. The methodology and results of PA monitoring are discussed in depth in chapter 7.

Assessment of whole-body exercise performance

Subjects performed a symptom-limited, maximal, incremental cycle ergometery test. This involved patients sitting on a static bicycle whilst having a mouthpiece held in their mouths and a nose peg to create a seal (see figure 3.7). The mouthpiece collected breath-by-breath measurements of gas exchange and ventilation during the ergometry test. Specifically, resting and peak measures of minute ventilation [VE (l/min)], oxygen consumption [VO_2, mls/kg/min)], carbon dioxide production [VCO_2, (l/min)] and work (W). The ergospirometry system used was the zAn-600 ErgoTest (ZAN Meβgeräte GmbH, Oberthulba, Germany). Resting and peak measures of blood pressure, SpO_2, HR, Borg breathlessness levels and Borg RPE levels were also collected.

Subjects were asked to remain still for one minute whilst resting values were collected. They were then asked to start a cycling warm-up; there was no load/ resistance on the bike at this time. This warm-up lasted for one minute for COPD patients and two minutes for healthy controls. Subjects were then informed that the resistance of the cycling would gradually increase. A ramp protocol was utilised, ensuring a steady linear increase in load over time. For COPD subjects the increase was 10W per minute (W/min) and for healthy

subjects the increase was 20 W/min. The difference in warm-up times and loads for patients and controls is standard practice in our laboratory; designed so that patients and controls perform the test for a similar duration. Subjects were asked to cycle at a cadence of 40-50 revolutions per minute (RPM) which was visible to them.

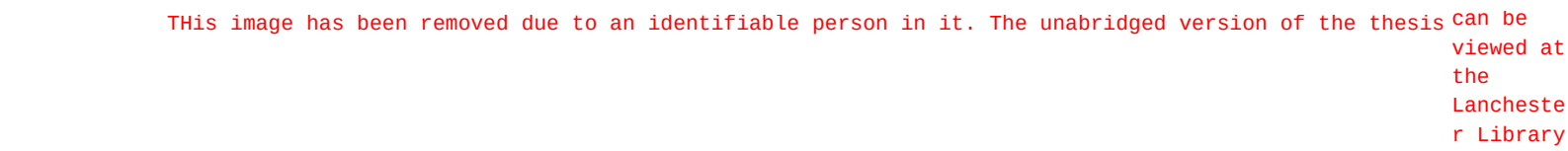


Figure 3.7 Maximal cycle ergometry test

The test ended when the subject could no longer continue due to symptom provocation, such as breathlessness or leg fatigue. The test could also be stopped by the operator if the subject was unable to maintain the required speed or if they believed that the subject was in any danger. The reason for terminating the test was recorded.

Assessment of Lung Function

At baseline only spirometry was performed by a trained technician in the Respiratory Physiology Department at Glenfield Hospital. Both COPD patients and healthy controls underwent these tests.

Basic spirometry was performed using the SPIRO AIR® spirometer with Exp'Air software (Medisoft: PAE de Sorinnes, Belgium). This involved the subject taking a maximal inspiration then blowing as hard and as fast as they could into the spirometer mouthpiece. A nose peg was also worn to prevent an air leak. Subjects remain seated throughout testing. FEV_1 (l), FVC (l) and the FEV_1/FVC ratio were recorded.

3.9 Equipment calibration

The isokinetic dynamometer, DEXA scanner, cycle ergometer and respiratory physiology equipment described in this methodology chapter all required calibration. For the isokinetic dynamometer this occurred monthly, whilst the DEXA, cycle ergometer and spirometry equipment were calibrated on each use. See appendix 12 for full calibration procedures.

3.10 Data acquisition, storage and statistical analysis

Acquisition, analysis and storage of data

Raw data (standard cybex output data) was collected manually and stored in the subjects' study notes for the RT results and for strength, muscle mass, cycle ergometry and questionnaire outcomes. A printed results sheet was

provided by the Respiratory Physiology department for all lung function results. These were filed in the subjects' study notes. The activity monitor data was acquired, stored and analysed using the ActiTrac software (IM Systems, Baltimore, USA). Electronic data was automatically saved on the isokinetic dynamometer, DEXA scanner and cycle ergometer for future use. These three systems were also backed up to an external hard-drive at least monthly. Results of all outcomes at baseline, mid-point and post-intervention were manually inputted into a statistical package (Statistical package for the Social Sciences: SPSS, version 16.0 and later version 17.0= PASW). The RT data from each training session was also inputted into SPSS for analysis. The data stored in SPSS was stored on two hard drives of a NHS computer (Dell Optiplex 745, Dell Inc, Austin, Texas, U.S) and three memory sticks, in separate locations.

Subjects' study notes were locked in a secure filling cabinet and computer equipment was also secure and password protected.

Power calculation

Statistical advice was taken from the Trent Institute for Healthcare Services Research at the time that the protocol was written. The main outcome measure chosen in this thesis was muscle strength, as this is an outcome for which we have previous data. Strength is also an important functional outcome for patients. We therefore estimated the samples size required to meet the study objectives using expected improvements in isometric muscle strength. From previous studies of RT in COPD patients we can estimate that

a 20% difference between groups or a 20% improvement in isometric quadriceps strength after training would be significant (Bernard et al. 1999;Spruit et al. 2002). Using quadriceps strength data obtained at our institution, we would require 24 subjects in each group to complete the study (90% power, significance level 0.05) to show a 10.0 (SD 14.8) Nm within-group improvement in isometric strength (Deacon et al. 2008). Allowing for a 25% dropout rate in the COPD group (the average for the outpatient rehabilitation programme at Glenfield Hospital) we would need to recruit 31 patients with COPD (per group) and 24 healthy controls.

Statistical analysis

All analysis was performed using SPSS version 16.0 and later PASW version 17.0. An intention-to-treat analysis was planned for subjects who completed the RT but dropped out of supplementation. The level of statistical significance was set at $p<0.05$. All data was firstly assessed for normality to choose appropriate parametric and non-parametric tests. Continuous and normally distributed variables are presented as mean and standard deviation. Categorical variables and skewed data are presented as medians and inter-quartile range or frequencies and percentages.

The strength of association between variables was assessed using Pearson's correlation coefficient for parametric data and Spearman's rank correlation for non-parametric data. To compare the agreement between two methods of clinical measurement Bland and Altman statistical methods were performed

(Bland & Altman 1986). Test re-test reliability was reported using the intra-class correlation co-efficient (ICC).

Comparisons within and between groups were analysed with paired and unpaired t-tests for parametric data and with Wilcoxon and Mann-Whitney U tests for non-parametric data. Appropriate post-hoc tests were chosen to evaluate were significant differences lay. When comparing more than two groups at one time point, a one-way analysis of variance (ANOVA) was performed (or Kruskal-Wallis for none-parametric data). When comparing more than two groups over time, a repeated-measures ANOVA with Bonferroni corrections for multiple comparisons was executed or a Friedman test for non-parametric data using time and group interactions. Generalised estimating equation (GEE) analysis was performed to compare the gradients of slopes.

Advice on the statistical analysis of this study was provided by the East Midlands Research Design Service (RDS) and Coventry University. Detailed statistical procedures are described in the individual chapters (4-7).

Chapter 4

Main randomised controlled trial outcomes; the role of supplementation as an adjunct to resistance training

4.1 Introduction

Resistance training (RT) is recognised as a key component of modern Pulmonary Rehabilitation (PR) programmes and, as such, is recommended within several international guidelines (Nici et al. 2006;Ries et al. 2007). This is because of the known associations between muscle weakness, healthcare utilisation and mortality (Marquis et al. 2002;Swallow et al. 2007b). Several investigators have shown that RT can improve muscle mass and strength in healthy elderly people (Brown et al. 1990b;Hakkinen et al. 2000) and in those with COPD (Bernard et al. 1999;Spruit et al. 2002). Improvements are generally in the region of 20% (Bernard et al. 1999;Spruit et al. 2002). From literature in healthy subjects, we know that changes in muscle mass, in response to training, tend to fall short of the increases in strength (Jones et al. 2004). This is because muscle force is not simply a product of muscle CSA, but also a number of other factors (discussed in chapter 2).

For the benefits of RT to be translated into muscle hypertrophy, sufficient protein substrate is required within the muscle to enhance muscle building. Dietary protein has been shown to induce protein synthesis in healthy young adults. However there is an impaired response in healthy elderly subjects and merely providing dietary protein may not be effective in increasing protein

synthesis (Cuthbertson et al. 2006). It may be that an anabolic stimulus, such as exercise is needed. In addition, the timing of supplementation in relation to resistance exercise may also be an important factor in the response for older people. Data from Denmark found that muscle hypertrophy only occurred in a healthy elderly group receiving protein immediately after RT and not in those receiving the protein two hours later (Esmarck et al. 2001). The aim of this thesis was to translate these observations to a group with COPD as the role of protein in combination with RT has not been studied in this population. Furthermore we do not know if the results will translate into functional benefits for patients. This was a mechanistic study, exploring the role of protein as an adjunct to RT. It was not a study of dietary protein in patients, in isolation, or alongside generic rehabilitation.

This chapter presents results from the main RCT as described in chapter 3.

4.2 Hypothesis and aim

Hypothesis

Resistance training, in combination with protein ingestion (at the time of training) will have greater effects on functional outcomes than resistance training alone.

Aim

To measure the functional response to the intervention at 8-weeks in terms of changes in muscle strength, muscle mass and whole-body exercise performance.

4.3 Methods

The methodology for the main study is described comprehensively in chapter 3- *materials and methods.* Refer to chapter 3 for details regarding recruitment, study design, randomisation, interventions and outcome measures. The power calculation identified that 24 subjects were required per group (90% power).

For ease of reading; the interventions and outcomes are summarised below.

Intervention groups

Patients with COPD and healthy controls all underwent 8-weeks of quadriceps RT using an isokinetic dynamometer. Training consisted of three supervised, 30-minute sessions per week. Subjects then performed five sets of 30 maximal knee extensions. The contractions were isokinetic and concentric at a PAV of 180°/sec. Each set was separated by a minutes rest and both legs were trained. The highest recorded peak torque (Newton-metres: Nm) and total work done (Joules: J) from the five sets was recorded for each leg. Completion was defined as those attending all 24 training sessions and presenting for their 8-week assessment visit.

COPD subjects were also randomly assigned to receive either a dietary protein (with carbohydrate) supplement or a placebo at the point of training throughout the study period. Healthy volunteers received the placebo only, as the role of protein alongside RT is already established in this group (Esmarck et al. 2001). Supplementation took place immediately after each training session and all subjects were responsible for making up their own drinks with water, under supervision.

Outcome measures

Outcome measures were assessed at baseline, after familiarisation and after 8-weeks of RT. The outcomes can be broadly classified into two categories:

Muscle function

- body weight
- total body fat-free mass (and FFM index)
- thigh lean mass
- isometric peak torque
- isokinetic peak torque (Nm) and total work (J) at a PAV of 60°/sec
-

Physical performance

- physical activity (convenience sample- results in chapter 7)
- whole-body exercise performance (cycle ergometry outcomes)

Measures of muscle function were also taken at the mid-point of training (4-weeks). This data is reported in chapter 5 where the relationship between outcomes and training intensity is examined.

4.4 Statistical analysis

Statistical analysis was performed using the statistical package for the Social Sciences: SPSS, version 16.0 (and later version 17.0= PASW). The level of statistical significance was set at $p<0.05$. Results are presented for those who completed the course of RT. An intention-to-treat analysis was planned for subjects who completed the RT but dropped out of supplementation. However, no subjects fell into this category.

Firstly the baseline characteristics were compared between completers/ non-completers in each group, to check for differences using an independent samples t-test (or chi-squared test for categorical variables). A one-way ANOVA with post-hoc Bonferroni tests was used to compare baseline characteristics and baseline outcome measures between the three groups (COPD supplement, placebo and controls). The equivalent test for non-continuous variables (e.g. gender) was performed using hierarchical loglinear analysis. Any baseline differences between the two COPD groups or between completers/ drop-outs were used as covariates in subsequent analysis (analysis of covariance: ANCOVA). The strength of association between variables at baseline and after RT was evaluated using Pearson's correlation coefficient for parametric data and Spearman's rank correlation for non-parametric data. In general, the correlation coefficient (r) represents the

strength of a relationship, values of: ±0.2 are weak, ±0.5 are moderate and ±0.8 are strong (Zou et al. 2003).

Comparisons between and within-groups were analysed with un-paired and paired t-tests for parametric data and with Mann-Whitney U tests or Wilcoxon tests for non-parametric data, respectively. When comparing more than two groups (i.e. COPD supplement, placebo and controls) at one time point, a one-way analysis of variance (ANOVA) with post-hoc Bonferroni test was performed (or Kruskal-Wallis for non-parametric data). The effect size for changes in outcome measures after the intervention was calculated by dividing the mean difference by the standard deviation of the pre-intervention measurement. By calculating effect sizes, the magnitude of change can be judged using the following criteria: small; 0.2 to 0.5, moderate; 0.5 to 0.8 and large; >0.8 (Cohen 1988).

It was hypothesised that wasted patients might respond differently to the intervention; patients were therefore stratified by FFM in the randomisation process. A post-hoc subgroup analysis of the main study outcomes was performed in patients with muscle wastage according to accepted FFMi criteria (i.e. <15kg/m^2 for women and <16kg/m^2 for men).

4.5 Results

Screening data, numbers recruited and attrition

107 participants (81 COPD/ 26 healthy controls) were recruited to the study after screening more than 500 patients for eligibility (see consort diagram-

figure 4.1). The reasons for exclusion from/ none-uptake to the study are shown in figure 4.2. The main reasons for COPD participants not meeting inclusion criteria were an MRC dyspnoea grade ≤2, unable to have a muscle biopsy (e.g. taking warfarin) and recent exacerbations.

After consent but prior to treatment allocation/ starting training: seven patients with COPD and one control withdrew from the study, five participants were withdrawn by the researcher as exclusion criteria (3 controls) had been met and one patient with COPD died (reasons for withdrawal are shown in figure 4.1). Therefore 71 patients with COPD and 22 controls started the RT programme. 38 patients with COPD were randomly assigned to the supplement and 33 to the placebo. In the supplemented COPD group, four participants were lost to follow-up and four discontinued the intervention. Therefore data from 30 subjects was available for analysis at the 8-week time point. For the placebo COPD group, two were lost to follow-up and two discontinued the intervention, leaving 29 available at the 8-week assessment. Reasons for loss at follow-up and discontinuation are shown in figure 4.1.

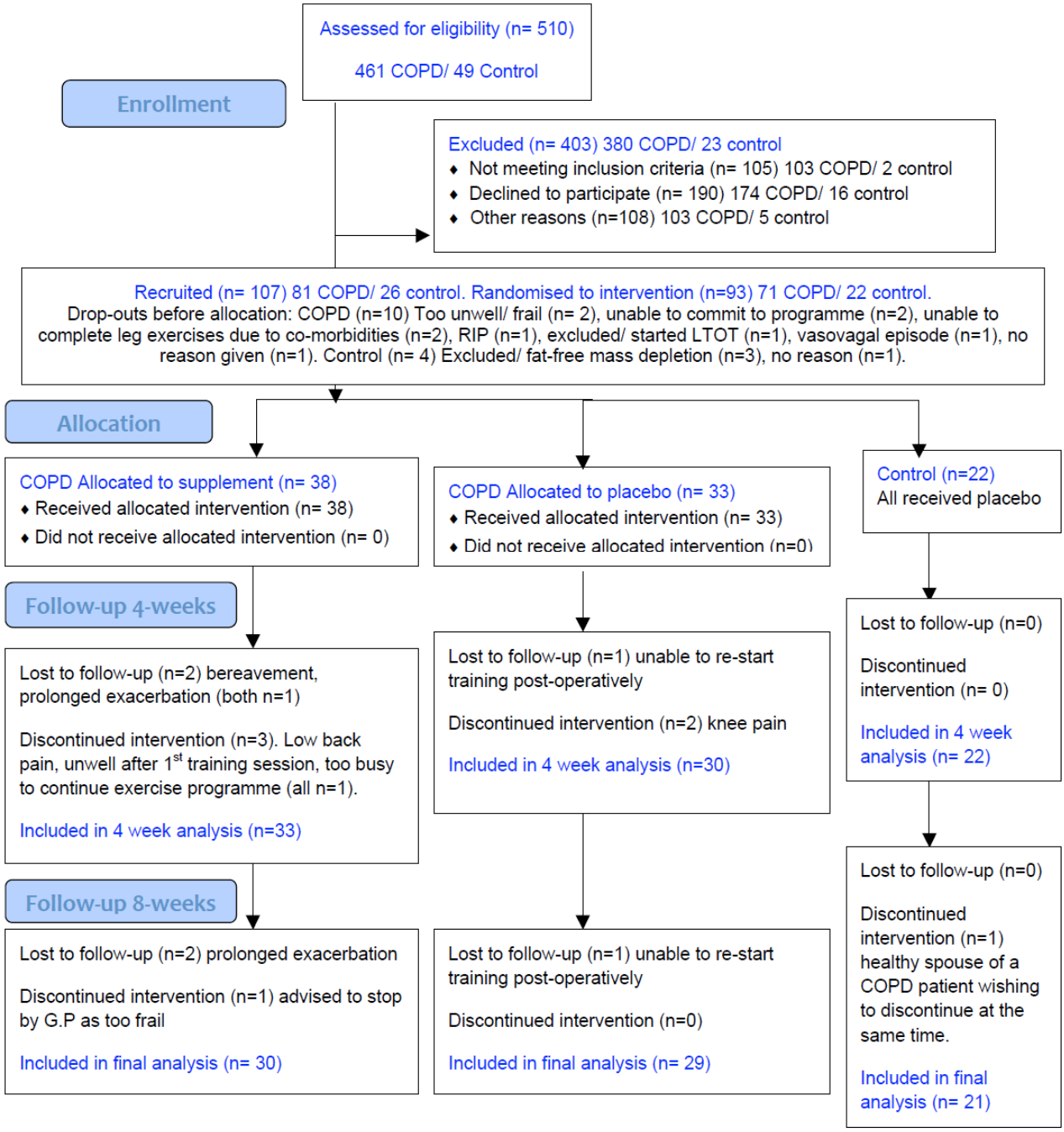


Figure 4.1 CONSORT flow diagram of study participants.

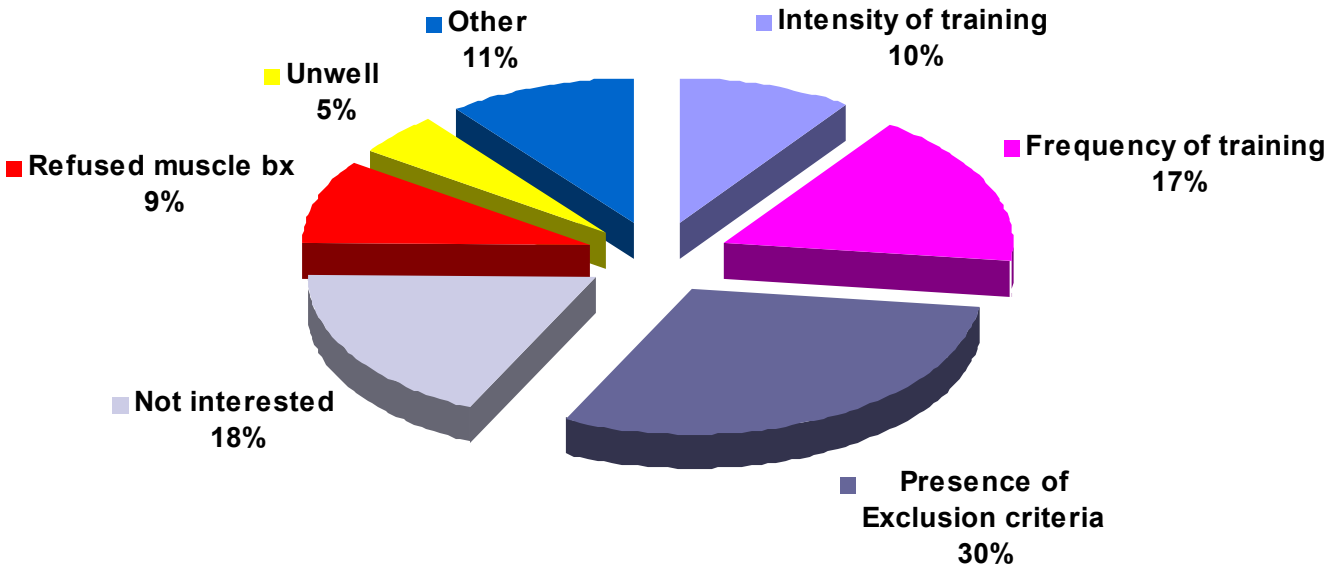


Figure 4.2 Reasons for exclusion from and none-uptake to the study

There was one discontinuation in the control group (spouse of a COPD subject who wanted to withdraw at the same time as their partner) and no loss to follow-up. More patients dropped out from the supplemented COPD group (n=8) compared to the placebo (n=4) and control (n=1) groups. However this was not statistically significant (chi-squared test, $p>0.05$ supplement vs. other two groups). This can be attributed to an increased number of disease exacerbations in this group (n=3 vs. n=0 in the other two groups).

There was full compliance with all patients ingesting their supplement or placebo drink after each RT session, under supervision of the researcher. Every subject who attended the 8-week assessment visit, completed all 24 RT sessions.

Baseline characteristics

The baseline characteristics of the three groups are shown in table 4.1. There were no significant differences in the baseline characteristics of completers and non-completers in the COPD groups. Pack years smoking was significantly different between control completers [mean (SD) 12.8 (21.5) years] and the one drop out in the control group (60 pack years) who was a current smoker ($p<0.05$). There were significant differences at baseline between controls and both COPD groups for MRC grade, smoking status, pack years, lung function variables and the number with defined muscle wastage (table 4.1), as expected.

Table 4.1 Baseline characteristics of the three treatment groups

	COPD Supplement n= 38	**COPD Placebo n= 33**	**Healthy Controls n=22**
Age (years)	68.6 (9.7)	67.7 (8.7)	66.5 (5.1)
Gender- number of males (%)	24 (63)	18 (55)	11 (50)
BMI	26.7 (4.9)	26.3 (5.6)	26.8 (2.8)
MRC Dyspnoea Grade- median (IQR)	3 (1)**	4 (1)**	1 (0)
Current smokers- number (%)	6 (16)*	8 (24)*	4 (18)
Smoking pack years (years)	48.5 (42.3)**	47.8 (31.0)*	14.9 (23.3)
FEV_1 (litres)	1.2 (0.4)**	1.2 (0.4)**	2.6 (0.7)
FEV_1 (% predicted)	47.0 (18.4)**	47.5 (16.9)**	104.8 (21.2)
FEV_1/ FVC (ratio)	39.9 (13.9)**	42.5 (11.7)**	72.1 (6.6)
Muscle wasted- no. (%)	7 (18)*	7 (21)*	0 (0)

All data are mean (± SD) unless otherwise stated.
***p<0.05; **p≤0.001 significant difference compared to control group.**

However there were no significant differences between control and COPD groups for age, gender and BMI. Furthermore there were no significant

differences between the two COPD groups at baseline for any variable (all p>0.05).

Baseline outcome measures

Table 4.2 displays the baseline values for the muscle function and physical performance variables measured in the three groups.

Table 4.2 Baseline values for muscle function and physical performance measures in the three treatment groups

	COPD Supplement n= 38	**COPD Placebo n= 33**	**Healthy Controls n=22**
Weight (kg)	72.4 (15.8)	71.2 (17.0)	73.1 (10.2)
Total body FFM (g)	48005.1 (9614.1)	47529.1 (10360.0)	48136.6 (9292.6)
Total body FFMi	17.6 (2.7)	17.5 (2.7)	17.5 (1.8)
Thigh lean mass (g)	4162.2 (975.3)	4093.8 (1139.9)	4446.3 (899.8)
Isometric strength (Nm)	111.0 (44.9)*	109.7 (47.6)*	137.7 (43.8)
Isokinetic peak torque (Nm) at 60°/sec	81.5 (35.4)	76.4 (34.3)**	99.7 (36.3)
Isokinetic total work (J) at 60°/sec	310.5 (145.5)	283.8 (141.9)**	378.6 (149.3)
Cycle ergometry work (W)	48.4 (21.1)**	52.3 (24.1)**	119.7 (38.3)
Cycle ergometry time (sec)	352.0 (128.3)**	372.1 (147.8)*	467.8 (129.8)
Cycle ergometry peak VO_2 (l/min)	1.1 (0.6)**	1.1 (0.5)**	1.7 (0.5)
Cycle ergometry peak VO_2 (mls/kg/min)	15.0 (6.1)**	15.0 (5.1)**	22.8 (6.3)
Cycle ergometry peak VCO_2 (l/min)	0.9 (0.3)**	1.0 (0.5)**	1.8 (0.7)
Cycle ergometry peak VE (l/min)	32.1 (10.7)**	32.2 (12.6)**	46.0 (17.2)
Cycle ergometry peak RER (l/min)	1.0 (10.7)**	1.0 (12.6)**	1.0 (0.1)

All data are mean (± SD). *p<0.05; **p≤0.01 significant difference compared to control group.

There were no significant differences between the three groups at baseline for weight, total body lean/ FFM and thigh lean/ FFM (all p>0.05). Control

subjects recorded significantly greater results in all cycle ergometry variables, compared to both COPD groups.

There was a significant difference at baseline between control subjects and COPD subjects receiving the placebo for isometric strength, isokinetic torque and isokinetic work. COPD subjects receiving the supplement however, only differed from controls for isometric strength ($p<0.05$). There were no significant differences between the two COPD groups, for any outcome at baseline.

From DEXA analysis, osteopenia was detected in 19 males (45%) and 16 females (55%) with COPD. Osteoporosis occurred in 5% of males (n=2) and 10% of females (n=3) with COPD. Diagnosis was based upon the World Health Organization T score criteria of -1 to -2.49 for osteopenia and ≤-2.5 for osteoporosis (World Health Organization 1994). These patients were advised to see their GP and a letter detailing the findings was sent to participants' GP with consent. No control subjects had evidence of bone thinning.

Baseline correlations in outcome measures

In COPD subjects there were weak but statistically significant correlations between FEV_1 (l) and total body lean mass (r=0.39 supplement/ r=0.38 placebo), quadriceps lean mass (r=0.44 supplement) and whole body exercise work performed at baseline [r=0.35 supplement/ r=0.43 placebo) all $p<0.05$].

Quadriceps (thigh) lean mass (g) was strongly and significantly correlated with both isometric strength (r=0.85) and isokinetic peak torque (r=0.85) in healthy controls ($p<0.001$) at baseline. The relationship between baseline thigh lean mass and isometric strength was moderate in subjects with COPD (r=0.67 supplement, r=0.64 placebo, both $p<0.001$). Thigh lean mass and isokinetic strength was also moderately correlated in patients with COPD at baseline (r=0.66 supplement, r=0.65 placebo, both $p<0.001$). Interestingly, thigh lean mass was also associated with cycle ergometry performance (work). Correlation coefficients were 0.75 (controls, $p<0.001$), 0.40 (COPD supplement, $p<0.05$) and 0.74 (COPD placebo, $p<0.001$). Furthermore, isometric and isokinetic strength were shown to be moderately related to ergometry workload performance in all groups [controls: r=0.78 (isometric) r=0.79 (isokinetic); supplement: r=0.5 (isometric) r=0.60 (isokinetic); placebo: 0.58 (isometric) 0.64 (isokinetic). All $p<0.001$].

Within-group changes and between group differences after the intervention

Results are displayed for those completing the assessments at the 8-week time point. Table 4.3 summarises the within-group changes (mean change from baseline ± 95% CI) for the main outcome measures after 8-weeks, in all groups.

Table 4.3 Mean change from baseline (95% CI) in outcomes after 8-weeks in all groups

	COPD Supplement n= 30	**COPD Placebo n= 29**	**Healthy Controls n= 21**
Weight (kg)	-0.8 ** (-1.5 to -0.2)	-0.4 † (-0.9 to 0.2)	-1.7 *** (-2.5 to -0.9)
Total body FFM (g)	50.6 (-327.3 to 428.5)	199.1 (-137.7 to 536.0)	29.5 (-373.1 to 432.1)
Thigh lean mass (g)	180.1 *** (102.2 to 258.0)	230.4 *** (140.0 to 320.7)	232.6 *** (154.1 to 311.2)
Isometric strength (Nm)	19.6 *** (12.2 to 27.0)	16.6 *** (9.5 to 23.6)	16.8 * (4.8 to 28.8)
Isokinetic peak torque (Nm)	17.7 *** (10.2 to 25.2)	19.8 *** (13.0 to 26.6)	12.8 * (4.0 to 21.5)
Isokinetic total work (J)	72.7 *** (35.9 to 109.6)	79.4 *** (52.2 to 106.6)	53.5 ** (13.0 to 93.9)
Cycle ergometry work (W)	9.9 * (4.2 to 15.7)	8.2 * (3.5 to 12.8)	13.9 *** (7.0 to 20.8)
Cycle ergometry time (sec)	60.9 *** (27.4 to 94.3)	49.0 ** (19.2 to 75.9)	58.1 ** (22.4 to 93.7)
Cycle ergometry peak VO_2 (mls/kg/min)	-0.5 † (-1.9 to 2.8)	2.3 * (0.1 to 4.5)	4.9 * (1.2 to 8.6)
Cycle ergometry peak VCO_2 (l/min)	0.3 (-0.1 to 0.8)	0.5 (-0.2 to 1.2)	0.4 * (0.0 to 0.7)
Cycle ergometry peak VE (l/min)	1.2 (-3.5 to 5.9)	5.6 (-0.1 to 11.2)	11.7 ** (4.4 to 18.9)

All data are mean change (95% CI). *p≤0.05; **p≤0.01; ***p≤0.001 significant difference within groups. † significantly different to control subjects (p≤0.05).

All groups made significant within-group changes in thigh lean mass, quadriceps strength and cycle ergometry peak work/ time. Change in weight at 8-weeks was significantly different between controls and the placebo COPD group ($p<0.05$). All groups lost weight after RT; this was significant in the supplemented COPD group ($p\leq0.01$) and controls ($p\leq0.001$). Changes in whole body FFM (and the FFMi) were small in all groups (<1% change from baseline) and did not reach statistical significance.

Table 4.4 shows the effect sizes for the changes in outcome measures after 8-weeks of RT in all groups. All within-group changes were small or moderate.

The only large effect size was for the change in cycle ergometry peak VO_2 in healthy controls [according to Cohen's definition (Cohen 1988)].

Table 4.4 Effect sizes for the change in outcome measures at 8-weeks in all groups

	COPD Supplement n= 30	**COPD Placebo n= 29**	**Healthy Controls n= 21**
Weight (kg)	-0.1	-0.0	-0.2
Total body FFM (g)	0.0	0.0	0.0
Thigh lean mass (g)	0.2	0.2	0.3
Isometric strength (Nm)	0.4	0.3	0.4
Isokinetic peak torque (Nm)	0.5	0.6	0.3
Isokinetic total work (J)	0.5	0.6	0.4
Cycle ergometry work (W)	0.5	0.3	0.4
Cycle ergometry time (sec)	0.5	0.3	0.4
Cycle ergometry peak VO_2 (mls//kg/min)	-0.1	0.4	0.8
Cycle ergometry peak VCO_2 (l/min)	1.0	1.1	0.6
Cycle ergometry peak VE (l/min)	0.1	0.4	0.7

Effect sizes (Cohen 1988): 0.2 to 0.5 (small), 0.5 to 0.8 (moderate) and >0.8 (large)

There were no significant differences between the two COPD groups for the changes in all outcomes (see table 4.5). Therefore we can reject the study hypothesis as protein did not enhance the benefits of RT in this study.

Table 4.5 Mean differences (95% CI) between COPD supplement and placebo groups after resistance training

	Mean difference *	95% CI	p value
Weight (kg)	-0.5	-1.3 to 0.4	0.27
Total body FFM (g)	-148.5	-645.0 to 348.0	0.55
Thigh lean mass (g)	-50.3	-166.7 to 66.2	0.39
Isometric strength (Nm)	3.0	-7.0 to 13.1	0.55
Isokinetic peak torque (Nm)	-2.1	-12.0 to 7.9	0.68
Isokinetic total work (J)	-6.7	-51.8 to 38.4	0.77
Cycle ergometry work (W)	1.8	-5.4 to 8.9	0.63
Cycle ergometry time (sec)	11.8	-31.8 to 55.5	0.59
Cycle ergometry peak VO_2 (mls//kg/min)	-1.9	-5.0 to 1.3	0.12
Cycle ergometry peak VCO^2 (l/min)	-0.2	-1.0 to 0.7	0.72
Cycle ergometry peak VE (l/min)	-4.4	-11.7 to 2.9	0.24

*** supplement within-group change minus placebo within-group change**

Measures of thigh lean mass at baseline and 8-weeks, and percentage change from baseline are shown in figure 4.3. Again all three groups made significant improvements after the intervention; this was in the order of 5%. Differences between the groups were not significant.

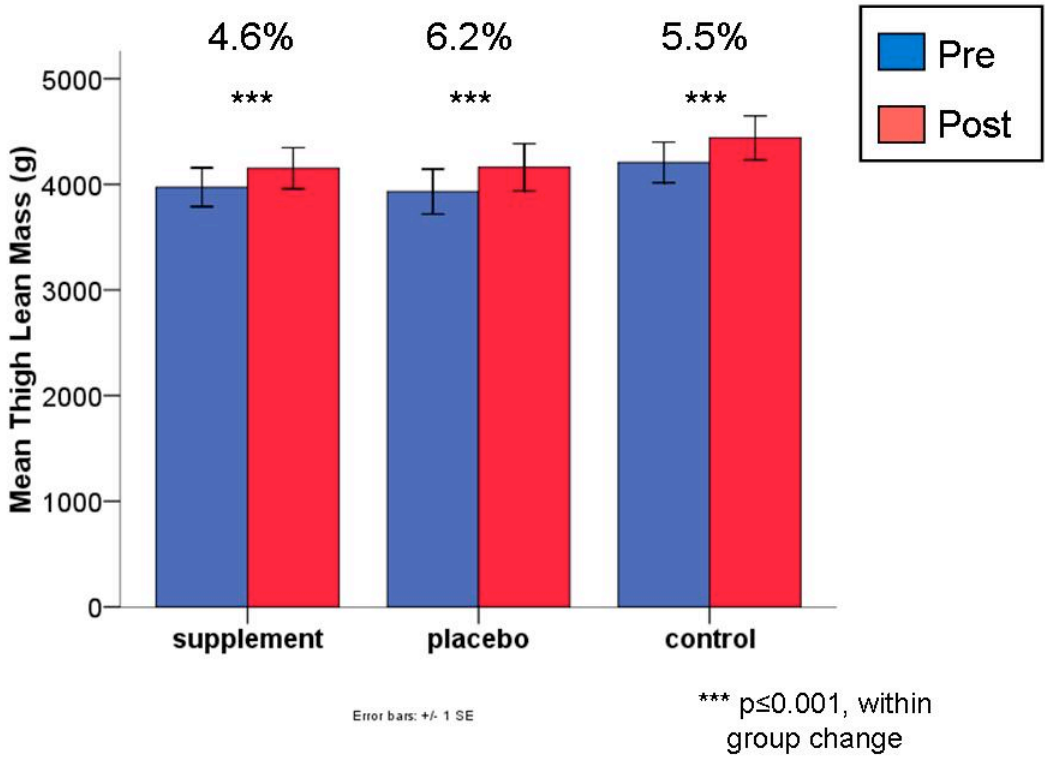


Figure 4.3 Percentage change from baseline in thigh lean mass in all groups

Figures 4.4 and 4.5 show the mean values for isometric and isokinetic strength (peak torque at 60°/ sec) respectively; before and after the intervention, in all groups. The percentage change from baseline is displayed across the top.

All groups made significant changes after 8-weeks in both measures of strength Both COPD groups had greater improvements in isometric and isokinetic strength, compared to controls. However there were no statistically significant differences between the groups. All groups had larger increases in isokinetic (dynamic) measures of strength (torque and work), rather than isometric (static) measures. The trajectory of change in quadriceps strength, in relation to training intensity, is examined further in chapter 5.

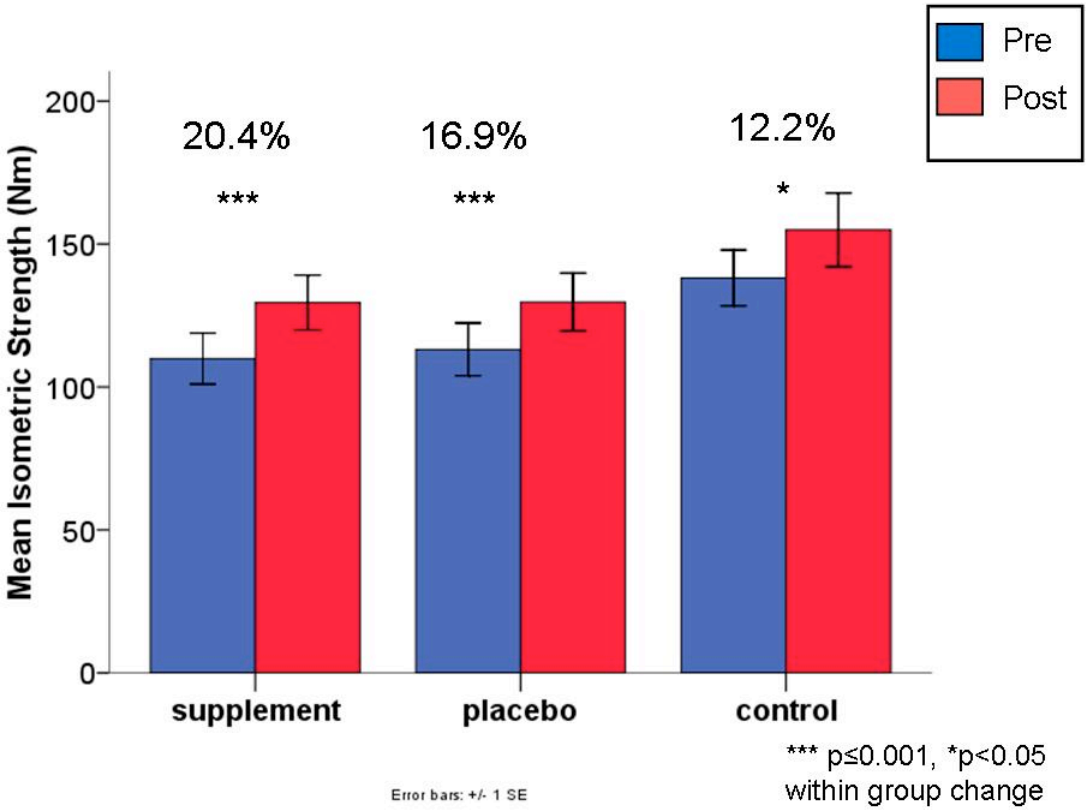


Figure 4.4 Percentage change from baseline in isometric strength in all groups

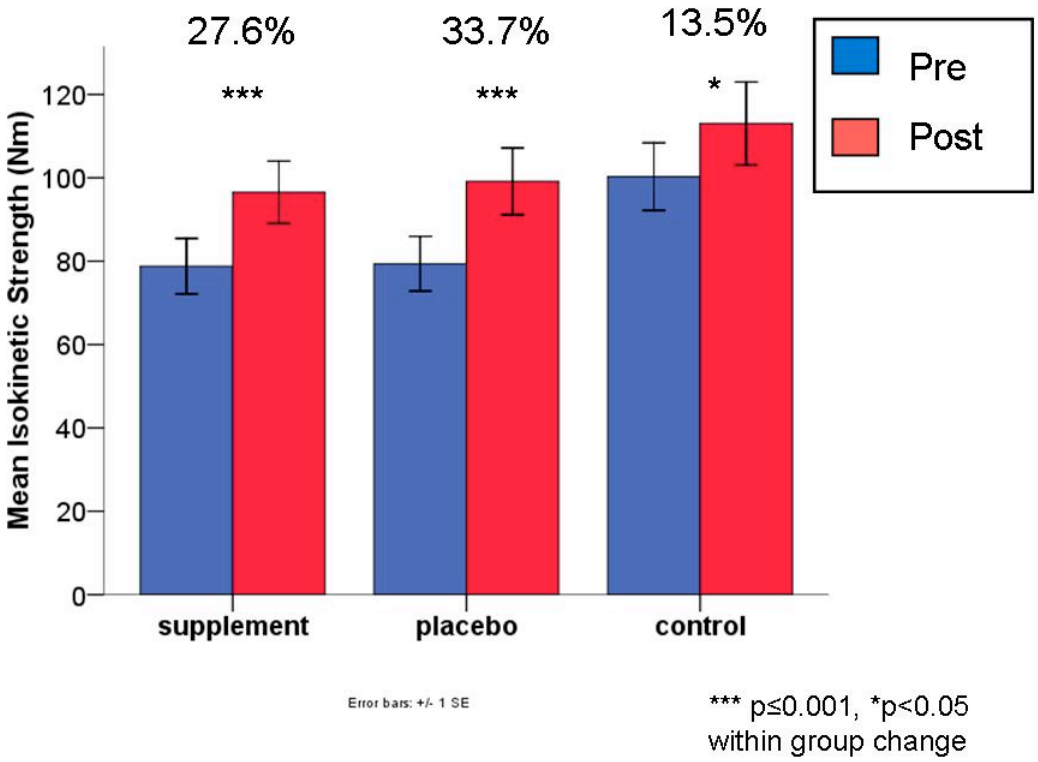
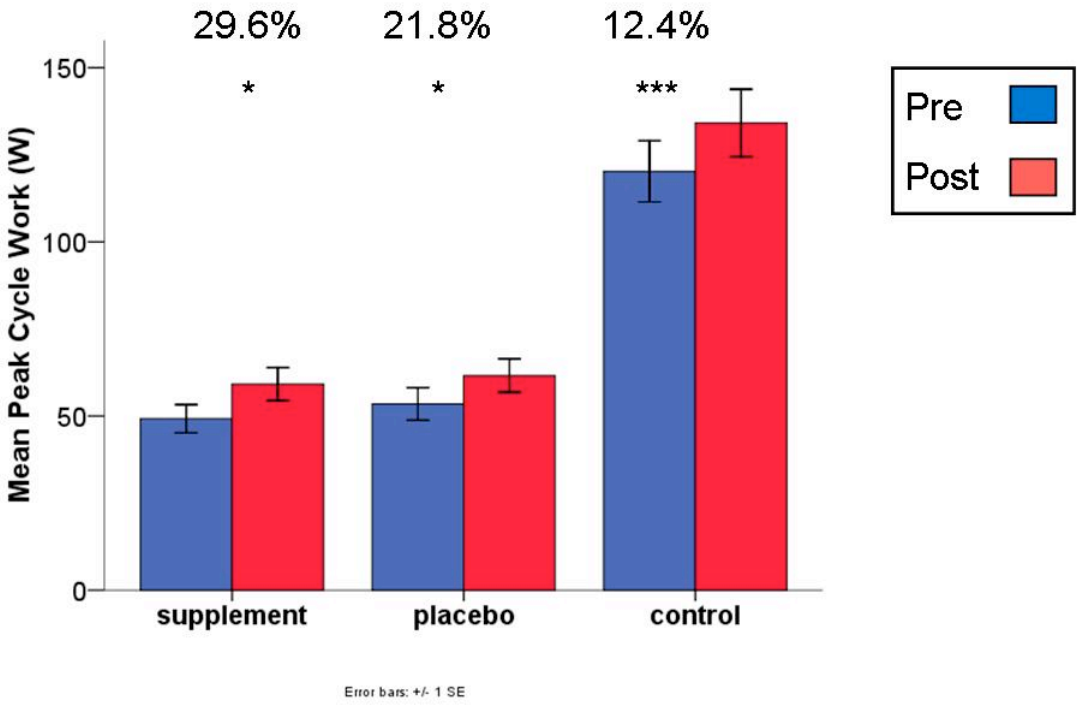


Figure 4.5 Percentage change from baseline in isokinetic strength in all groups

Changes in whole-body exercise performance indicate some carry over of RT to endurance performance. Peak cycle work improved in all three groups (figure 4.6- mean values at baseline and 8-weeks, and percentage change from baseline). The change was approximately 10 watts in each group and there were no significant differences between the groups.



NB. Control subjects had 20W/ min increase in load. ** p≤0.001, * p<0.05 within group change.

Figure 4.6 Percentage change from baseline in peak cycle work in all groups

Cycle time improved by around one minute in all groups. The change in peak VO_2 was significantly lower in the supplemented COPD group compared to controls ($p<0.05$) and only reached statistical significance in control and placebo COPD groups ($p\leq0.05$). There were no differences between the groups for any other cycle ergometry outcome. However, changes in VCO_2

and VE only reached statistical significance in the control group ($p \leq 0.05$ VCO_2 and $p \leq 0.01$ VE).

Correlations between changes in outcome measures after the intervention

Patients with COPD who received the supplement had significant associations between changes in weight and changes in thigh lean mass ($r=0.38$, $p<0.05$). Changes in isometric strength were moderately correlated with changes in isokinetic peak torque ($r=0.53$), isokinetic work ($r=0.45$) and cycle ergometry work [($r=0.40$) all $p<0.05$). Furthermore changes in cycle work were also correlated with isokinetic peak torque ($r=0.60$) and isokinetic work [($r=0.56$) both $p<0.01$] in supplemented COPD subjects.

For the placebo COPD group, the only significant associations were between changes in isometric strength and changes in isokinetic peak torque ($r=0.72$) and isokinetic work [($r=0.61$) both $p<0.01$].

In control subjects, changes in isometric strength were strongly correlated with changes in isokinetic peak torque ($r=0.83$) and work [$r=0.76$ (both $p<0.01$)]. Also changes in cycle ergometry work and changes in peak VO2 were strongly correlated ($r=0.83$, $p<0.01$).

Sub-group analysis of wasted and non-wasted patients with COPD

Supplement and placebo groups collapsed

A post-hoc subgroup analysis was performed to compare wasted and non-wasted subjects with COPD with the supplementation (protein and placebo) groups collapsed. Twelve subjects had FFMi evidence of muscle wastage. The remaining 47 patients with COPD who completed the study had no evidence of muscle wastage. The wasted and non-wasted subgroups were different at baseline for weight, BMI, FFM, FFMi, isometric and isokinetic strength and cycle ergometry work (all significantly lower in the wasted group, all $p \leq 0.05$). These factors were used as covariates in the analysis. Wasted patients made significantly less improvement in isometric quadriceps strength (15.1 Nm difference between groups), isokinetic quadriceps strength (15.3 Nm difference between groups) and whole-body work (9.8 W difference between groups), compared to non-wasted patients (all $p<0.05$). However these results should be interpreted with caution, as the numbers in the wasted sub-group are probably too small to make meaningful comparisons.

There were no significant differences between wasted and non-wasted groups for any other outcome (besides quadriceps strength and cycle ergometry work).

Comparing supplemented and placebo groups

When further sub-division of the wasted and non-wasted groups occurred, taking supplementation into account, this left only six subjects in both the

wasted supplemented and wasted placebo groups. These groups are probably too small to detect significant differences and there were no significant differences detected between supplemented and placebo groups, for any outcome when divided into FFMi sub-groups.

4.6 Discussion

This chapter reports the results of a RCT of protein supplementation in patients with COPD, undergoing RT. This is novel, as the role of protein as an adjunct to RT has not before been studied in this population. The primary aim was to measure the functional response to the intervention at 8-weeks in terms of changes in muscle strength, muscle mass and whole-body exercise performance. The effects in patients with COPD are compared with healthy, age-matched controls. This again is unique as often healthy controls are trained and considered separately.

The results indicate that the study hypothesis can be rejected as there were no significant differences between the COPD subjects receiving the supplement or the placebo. Therefore supplementation sub-groups have been collapsed in subsequent chapters (5-8). All groups made significant within-group improvements in quadriceps strength, thigh lean mass and whole-body exercise performance. We can infer from these findings that the increases in muscle mass, evident in all groups, indicate that RT increased net protein synthesis within the quadriceps muscle. This in contrast to work by Cuthbertson and colleagues who found that providing dietary protein was not effective in increasing protein synthesis in elderly muscle (Cuthbertson et al.

2005). However this study (Cuthbertson et al. 2005) did not include a training programme which may be responsible for providing the necessary anabolic stimulus in the current study. It is not clear whether the RT programme used in this thesis activated protein synthesis pathways, inhibited protein degradation pathways or a combination of both. We know from previous research that RT can influence both protein synthesis and degradation (Phillips et al. 1997) and that there is evidence of increased whole-body protein turnover (increased rates of protein synthesis and breakdown) in patients with COPD compared to healthy controls (Engelen 2000). This may be clarified with the muscle biopsy analysis (performed by Dr Menon- analysis incomplete at the time of writing this thesis).

In the current study, providing additional protein at the time of RT did not enhance the benefits of RT in patients with COPD. The reasons for the failure of this intervention are unclear. It may be that the stimulus or signal from RT swamps any additional affect of protein. Alternatively the level of protein given may not have been enough to show an enhanced response, above RT alone. It could be that improvements are dependent on the dose of protein given and that this will differ for each individual (i.e. varies with gender, BMI etc). Steiner and co-workers have previously shown that an improvement in walking performance was related to the amount of carbohydrate ingested during a PR programme (Steiner et al. 2003). In the current study the same ‘dose’ of protein was given to all in the supplemented group and the level did not change over the course of RT. This may be a limitation. However in a study by a Danish study group, quadriceps muscle hypertrophy was significantly

improved in an elderly group who received protein immediately after RT and not in those receiving the protein two hours later [$p<0.001$ between timing groups (Esmarck et al. 2001)]. This is despite the subjects in the Danish study receiving less protein (10g) than the subjects in the current study (19g).

There was a trend towards subjects with COPD (both groups) making greater improvements in strength, thigh lean mass and whole-body exercise work and time, compared to healthy controls. However the differences between the three groups were not statistically significant. Interestingly, data from chapter 5 shows that the even the most disabled patients with COPD, who were performing RT at much lower intensities compared to healthy controls, can make comparable improvements in thigh mass, strength and whole-body exercise performance.

It may have been that because patients with COPD had lower baseline values for these outcomes that they had more scope to improve. Baseline values for isometric and isokinetic strength (at 60°/sec) fell far short, in patients with COPD, of expected values in healthy older persons (as outlined in table 2.4, *Literature Review*). Alternatively, there may have been a 'regression to the mean' effect (when baseline values are highly variable, subsequent results are closer to the actual mean). However this effect should have been minimised because all subjects were familiarised to the outcome assessments, prior to baseline testing.

This RCT was adequately powered to detect differences in the functional outcomes within the two COPD groups, however the required sample size was not met in the control group (n=21 completed, n=24 needed). In future, a between-group power calculation may be more appropriate for this study design. It was perhaps ambitious to expect no drop-outs in the control group and to therefore not allow for attrition within the power calculation. Furthermore, very small numbers of wasted patients were recruited (n=12 overall). Although the FFMi criteria are based on using BIA, this was unexpected, as work from our group has previously shown that around 50% of patients with COPD were deemed to have muscle wastage using the same DEXA criteria (Steiner et al. 2002). Indeed, DEXA generally detects more cases of FFM depletion when compared to BIA (Steiner et al. 2002). Therefore the results of the post-hoc sub-group analysis should be interpreted with caution, as it is likely that this analysis was underpowered to detect changes in the wasted group. None the less, the data suggests that the response to RT may be lower in the wasted patients and that additional protein was equally ineffective in both wasted and non-wasted groups. Using the arbitrary FFMi cut-off values was unhelpful when defining this COPD population. In future, it may be better to observe muscle mass as a continuous variable to look for obvious sub-groups.

RT resulted in weight loss for all groups. These reductions were only significant in the control and placebo COPD groups. Total body lean and FFM mass increased; therefore changes in weight can be attributed to changes in fat mass. Loss of lean or FFM is important to measure in the context of any

rehabilitation programme for patients with COPD where exercise may result in a negative energy balance (Baarends et al. 1997a). Steiner and co-workers have previously shown that an improvement in walking performance was related to the amount of carbohydrate ingested during a PR programme (Steiner 2003) and that a lack of carbohydrate may pose a limit to the amount of training patients can do. The same may be true of protein during RT or conventional PR. If patients with COPD are in a negative protein balance prior to training (wasted), they may require additional protein in the diet to ensure muscle protein synthesis. Some underweight patients with COPD show signs of heightened inflammation and progressive cachexia. These patients respond particularly badly to nutritional support (Creutzberg et al. 2000). A poor treatment response in these patients may be attributed to an inadequate assessment of their energy requirements when engaged in a rehabilitation programme (Baarends et al. 1997a). It may have been that some of our 'wasted' patients fell into this 'non-responder' category and therefore reduced the effect of protein supplementation in the whole group.

In clinical practice, it may be important to measure lean mass/ FFM before and during exercise programmes for patients with COPD. The reasons for this are two-fold: to ensure that adequate nutritional support can be given to overcome the metabolic demand of exercise and, secondly, to confirm that exercise is not exacerbating further lean mass loss. Indeed, the stimulus of exercise may be shown to improve weight gain by stimulating appetite. In the current study, habitual diet was not measured. This is perhaps a limitation as those assigned to the supplement group may have altered (decreased) their

normal dietary intake of protein to adjust for supplementation. This adjustment has been shown in previous studies of supplementation alongside rehabilitation in patients with COPD (Steiner et al. 2003). However this was a mechanistic study, examining the role of protein as an adjunct to RT. It was not a study of dietary protein in patients, in isolation, or alongside generic rehabilitation in patients with COPD. The primary hypothesis was to discover if providing additional protein at the time of training would lead to greater muscle protein synthesis and have greater effects on functional outcomes than RT alone.

Another potential limitation was that healthy controls only received a placebo following training; a second group did not receive the supplement. It could have been interesting to examine if protein provided any additional benefit to RT in control subjects, as protein had no effect in the COPD patients from this study. However, prior to starting the study we were aware of the effects of supplementation and RT in healthy, elderly subjects (Esmarck et al. 2001). Therefore it was not deemed necessary to provide control subjects with protein. Controls all received a placebo drink post-exercise so that their transition through the training programme (e.g. session time) was identical to patients with COPD. This was particularly important for healthy spouses who trained alongside their partners with COPD.

It is likely that the improvements in muscle function and physical performance were meaningful for many of the subjects with COPD, despite only small or moderate effect sizes calculated. However it is important to remember that

this was a motivated group of patients, keen to undergo exercise training. Therefore selection bias may have been a factor. Furthermore, the results may not be representative of a typical COPD population as the most severe patients (i.e. those of long-term corticosteroids and oxygen) were excluded. This was due to the biopsy procedure in the main study design.

There is no MCID established for changes in thigh mass, quadriceps strength or cycle ergometry outcomes in this population. This makes it difficult to interpret the findings, although we can compare these results to previous studies of RT in patients with COPD or healthy populations. The percentage change in thigh lean mass was approximately 5% in all groups; this is in keeping with the percentage of lean mass restoration observed after immobilisation in healthy men (Jones et al. 2004). It is, however, important to remember that their may have been some bias and measurement error in drawing the ROI for thigh mass on DEXA analysis. This could've been minimised by asking a blinded assessor to perform the drawing. The intra- and inter-operator variability in this measure is unknown and would be something to consider if using this measure again.

Changes in quadriceps strength are typical around 20% after PR in patients with COPD (Bernard et al. 1999;Spruit et al. 2002). Changes in isokinetic strength are seldom reported for the COPD population. In the current study, isometric and isokinetic strength exceeded 20% in the supplemented COPD group and the isokinetic strength change was more than 20% in the placebo COPD group. Changes in strength were greater in both COPD groups

compared to controls (percentage change <15% for isometric and isokinetic strength), although this was not statistically different. Also, changes in isokinetic strength were greater than changes in static strength (isometric) for all groups. This perhaps indicates that isokinetic or dynamic strength is more responsive to training. Alternatively, this may simply reflect a specific adaptation to the RT programme which was also isokinetic in nature. Previous studies in healthy individuals have confirmed that isokinetic peak torque improves at velocities above and below the training velocity (Kraemer, Mazzetti, Ratamess, & Fleck 2000). In this instance, although the training was at a PAV of 180°/sec, improvements have also occurred at the testing velocity of 60°/sec. Furthermore, isokinetic training can also improve measures of isometric strength (Kraemer et al. 2000); this is evident in the current study.

The changes in quadriceps strength, in all groups, are disconnected from changes in muscle mass, which were much lower after RT (around 5%). This highlights that other factors (besides increased mass) are involved in producing muscle force (Jones et al. 2004). Several authors have reported that neural adaptations within the muscle may account for this disconnect between strength and mass changes (Sale 1988). Neural adaptations are related to the quality and coordination of the muscular contraction and occur during the first few weeks of a RT programme (Moritani & deVries 1979). However, neural adaptations were not directly measured in the current study. Muscle hypertrophy (change in fibre/ muscle group size) occurs later as a result of long-term training (Sale 1988). Therefore, changes in thigh mass may have been greater if the RT were to continue beyond 8-weeks. Chapter 5

reports relationships between RT intensity and the outcome measures, with measurements also reported at the mid-point of training (4-weeks). Therefore chapter 5 may help to unravel when changes in quadriceps muscle mass and strength occur in the time course of a RT programme.

As well as improvements in muscle strength and mass, the RT programme also produced significant gains in whole-body exercise performance. Changes in quadriceps strength were associated with changes in cycle ergometry work for the three groups. The change was around 10 W for peak cycle work and one minute for peak cycle time, in all groups. However the improvements were lower in the placebo COPD group (8.2 W change, 49 second change; not significantly different to the other 2 groups). In a meta-analysis of 13 trials of cycle ergometry (Lacasse et al. 2006), the common effect size was 8.4 W following PR. Data from the NETT trial suggests an MCID of 4 W following pre-LVRS rehabilitation (Puhan et al. 2011). Therefore improvements in the current cohort exceed these suggested threshold values for ergometry work rate. However the MCID of 4 W from the NETT trial is not likely to be representative of a typical (stable) COPD population, as all subjects were pre-LVRS with worse disease severity. There were also significant improvements in peak VO_2 (mls/ kg/ min) for the supplemented COPD group and control subjects. VE and VCO_2 increases were only significant within the control group. These changes in whole-body exercise performance are perhaps surprising, given that RT is not routinely expected to influence endurance outcomes. However we know that lower-limb weakness contributes to whole-body exercise performance (Steiner et al. 2005). One may speculate that by

improving quadriceps strength, this may have meant that subjects were able to sustain cycling performance for longer, in the current study. Another plausible explanation is that the RT programme utilised in this study, activated the cardio-respiratory system. Although cardio-pulmonary stress and metabolic load is lower in RT when compared to endurance training (Probst et al. 2006) we can expect any form of exercise training to active the cardio-respiratory system to a certain extent. Particularly as the chosen speed for this study (180°/sec) sits in the middle of the spectrum of speeds available on isokinetic machines and, as such, represents the centre of the muscular strength to endurance continuum (Kraemer et al. 2000). Chapter 6 explores in more detail the cardio-respiratory load imposed by the RT programme chosen in the current study.

The attrition rate for the study was in line with our outpatient PR service for the COPD supplement group (26%) and much lower than expected in the placebo group (12%). The higher drop-out rate in the supplement group was due to a greater number of disease exacerbations. This probably occurred by chance and is not thought to be related to supplementation. Furthermore, the drop-out rates for the three groups were not significantly different to one another. The uneven drop-out rates meant that the two COPD groups had more even numbers at the end of 8-weeks, as the two COPD groups were uneven at randomisation (n= 38 supplement, n=33 placebo). This was due to the block randomisation procedure performed, because the blocks were of uneven sizes and not all blocks were used. The two COPD groups were well

matched at baseline and thigh mass was correlated with quadriceps strength and cycle ergometry work at baseline in all three groups.

In conclusion, this is the first study to explore the role of protein as an adjunct to RT in patients with COPD and to compare the results to a healthy, age-matched control group. The data suggests that all groups made significant within-group improvements in thigh lean mass and quadriceps strength after RT. These changes translated into whole-body exercise performance improvements; indicating some functional carry over from RT and suggest that the RT programme activate the cardio-respiratory system. Although there was evidence of increased protein synthesis within the muscle (increases in thigh lean mass), providing additional protein at the time of training, did not enhance the benefits. The reasons for this are unclear. Therefore, the universal prescription of protein alongside RT can not be routinely recommended for patients with COPD. In future, it may be important to adapt the dose and the timing of supplementation in relation to training to observe whether amending these factors can improve the outcome. As protein did not augment the benefits of RT, the supplement and placebo groups are collapsed from this point forward.

Post-hoc sub-group analysis in wasted patients revealed that the response to RT may be lower in this group. However, providing additional protein was equally ineffective in both wasted and non-wasted groups. Using the arbitrary FFMi cut-off values was unhelpful as we recruited very few wasted patients using this definition.

Chapter 5

Training intensity trajectory and fatigue profile of the resistance training programme. How does training intensity relate to functional outcomes?

5.1 Introduction

Chapter 4 reported the main outcomes from the RCT of RT and protein supplementation given at the time of training. As protein did not enhance the benefits of RT, the COPD sub-groups are pooled in this chapter. Interestingly, chapter 4 showed that patients with COPD made comparable improvements to healthy controls. This is despite anecdotally appearing to perform RT at a lower absolute intensity. The unique RT programme chosen in this RCT provided a novel opportunity to precisely explore the training intensity progression, fatigue profile and cardio-respiratory load imposed by the training; comparing patients with COPD to healthy controls. The cardio-respiratory load of the training is discussed in chapter 6.

Unlike endurance training or comprehensive PR, we do not know what the optimum ‘dose’ of RT is, to derive maximum benefit in terms of muscle strength and mass. The ‘dose’ comprises of training intensity and duration (Zuwallack et al. 2006). The relationship between RT intensity and outcome measures, such as strength has been poorly described in the COPD population. Ideally, the optimum ‘dose’ of training should depend on the individuals’ needs (related to baseline values) and the ongoing measurement

of outcomes during training (Ries et al. 2007). However the serial measurement of outcomes may be impractical in the context of a training programme. It is not apparent whether changes in muscle strength and mass, following RT, track the same trajectory as improvements in exercise tolerance and HRQoL derived from endurance training or comprehensive PR. Although we do know that progressive RT in healthy adults does improve maximal strength in a dose-dependant pattern (Steib, Schoene, & Pfeifer 2010). In the current study, there was the opportunity to observe the trajectory of change in training intensity and to relate this to outcome measures, recorded at 4 and 8-weeks.

Muscle fatigue is an important area of research as it is essential for daily living tasks and exercise performance. However, the term ‘fatigue’ has been poorly defined in the literature. The fatigue index (FI) is a common parameter described in and calculates the amount of muscle fatigue using the following equation: final force/ initial force x 100 (Thorstensson & Karlsson 1976). This index reflects the amount of force decay. The capacity to resist muscle fatigue during exercise is known as ‘fatigue resistance’ (FR). Generally, fatigue and FR are measured during strength testing (one session). However it may be important to look at these factors successively, during a RT programme. There is some data available in healthy (young and old) individuals to suggest that RT can improve FR (Campos et al. 2002;Izquierdo et al. 2006;Kemmler et al. 2004;Salvador et al. 2009). Furthermore, training until fatigue is thought to enhance strength outcomes (Abdalla, McGregor, & Strutton 2007;Izquierdo et al. 2006). The majority of studies exploring fatigue, derived from isokinetic

methods, have focused on peak torque (maximal strength) as an outcome, rather than work (cumulative). Therefore the fatigue characteristics of isokinetic work remain largely unknown in healthy and diseased populations.

There is some discrepancy in the literature regarding the effects of ageing on muscle fatigue. Some investigators suggest that older people experience greater muscle fatigue than younger counterparts (Cupido, Hicks, & Martin 1992;Petrella et al. 2005) whilst others argue that older people are more fatigue resistant than the young because ageing muscle relays more heavily on oxidative rather than glycoltic pathways and therefore lactate production is reduced (Lanza, Russ, & Kent-Braun 2004). Muscle fatigue, and particularly the FI, is seldom reported in studies of patients with COPD. However one study has shown that fatigue is reduced after a neuromuscular electrical stimulation (NMES) training programme (Neder et al. 2002).

This chapter aims to describe the training intensity trajectory and fatigue profile of this unique RT programme in patients with COPD. The benefit of using isokinetic dynamometry is that the profile of training has been accurately recorded over the 8-week training period in terms of total work performed and peak torque (at 180°/sec). Therefore training progression and force decay during training can be observed and related to changes in outcome measures at 4 and 8-weeks. In addition, a healthy age-matched control group also underwent the same training programme alongside patients with COPD. This allows for direct comparison of the training profiles in each group. This is distinctive, as often healthy populations are considered separately.

5.2 Aims

Three aims were formulated to establish, and compare, the training profile in patients with COPD and healthy age-matched controls. They were:

1. To observe the **trajectory** of change in isokinetic total work (J: at 180 °/sec PAV) and peak torque (Nm) performed over the 8-week training period.

2. To investigate the within-session **fatigue profile** of total work and peak torque (at 180°/sec) over 5 training sets, by calculating the force decay [fatigue index (FI)] over the 8-week training period.

3. To analyse the **relationship between training intensity and changes in outcome measures** at four and 8-weeks.

5.3 Methods

The methodology for the RCT discussed in this thesis is described in detail in chapter 3. This includes recruitment of subjects, details of the intervention and outcome measures assessed. Chapter 4 outlines the main outcomes of the RCT. As protein supplementation did not have augment the effects of RT, the results presented in this chapter are pooled for supplemented and placebo COPD groups.

Trajectory of RT

To observe the trajectory of improvement in RT over the training period, work and torque data were collected for both legs. Subjects were asked to perform

5 sets of 30 maximal knee extensions (concentric) at a PAV of 180°/sec, during each training session. There were 24 training sessions over the 8-week training period (3/ week). The highest peak torque was recorded from the 30 repetitions making up each of the 5 training sets. Work was cumulative over 30 repetitions. For simplicity, the data for the right leg only has been reported for all subjects (95.2 % of subjects were right leg dominant), however training took place bilaterally and data from the left leg is reported in appendix 13. The average torque and work per week is also shown in the graphs (i.e. training sessions 1-3 = week one, 4-6 = week two etc).

Fatigue Profile

The fatigue index (FI) was calculated to measure the decay in isokinetic work and peak torque (180°/sec) over the 5 sets of 30 repetitions. FI was calculated as set 5/ set 1 x 100. The FI was plotted as the average over weeks 1-8 as described above. The absolute decline in work and torque between sets 1 and 5 (average per week), is also reported. Again, data from the right leg only is presented.

Relationship between training intensity and changes in outcome measures

To assess the changes in quadriceps strength over the 8-week training period, both isometric and isokinetic strength (at the testing velocity of 60°/sec) of the dominant leg was measured using an isokinetic dynamometer at baseline (after familiarisation), at week four (training sessions 12-14) and at week eight (24 hours after the last training session). Peak isometric strength

(Nm) was measured during six attempts at a maximum static contraction, with the knee fixed at 70° flexion. Isokinetic strength was also assessed during two sets of five knee extensions at a PAVof 60°/sec. The highest peak torque (Nm) and total work done (J) for the best set was recorded. Thigh lean mass was measured using DEXA (g) at the same time points. Correlations between training loads and outcome measures are reported.

5.4 Statistical Analysis

The data is presented per-protocol, for subjects' data available at each time point (i.e. per training session/ per week for patients still engaged in RT).

Firstly graphs were produced to observe the **trajectory of change** in isokinetic total work and peak torque and (at 180 °/sec angular speed) over the 8-week training period; comparing patients with COPD and healthy controls. A repeated measures ANOVA was performed with Bonferroni corrections for multiple comparisons, to analyse within and between-group changes in work and work over weeks one to eight. Generalised estimating equation (GEE) analysis, also known as 'cross-sectional time-series analysis' was executed to calculate whether or not the graph slopes for training intensity (work and torque) in COPD subjects and controls were significantly different from one another (group x time interaction with Wald confidence limits). i.e. was the training trajectory for the COPD group different to that of the controls?

The **fatigue profile** was assessed by plotting the FI and the absolute decline in work and torque (averaged each week), using a repeated measures ANOVA, as described above.

The changes in outcomes (isometric strength, isokinetic strength at 60°/sec and thigh lean mass) between baseline and 4-weeks/ 8-weeks were compared within-groups and between groups using paired and independent t-tests, respectively. Also the **correlation between training intensity and changes in outcomes** at weeks four and eight were observed with scatter plots and associations analysed using the Pearson's correlation coefficient. The strength of any associations is as described in chapter 5 (i.e. weak/ moderate/ strong).

5.5 Results

70 patients with COPD [mean (SD) age 68.6 (9.1) years, BMI 26.7 (5.4), FEV_1 44.8 (15.2) % predicted, 42 male] and 22 healthy age-matched controls [mean (SD) age 66.6 (5.1) years, BMI 26.8 (2.9), FEV_1 103.4 (15.9) % predicted, 12 male] were enrolled as part of a RCT of protein supplementation (PS) alongside RT and started the training programme. There were 11 drop-outs in the COPD group (nine by 4-weeks) and 1 in the control group (lost between weeks four and eight). The main results of the RCT are provided in chapter 4. This chapter presents per-protocol data, for subjects' data available at each time point (i.e. per training session/ per week for patients still engaged in RT).

The number of subjects per week is outlined in table 5.1.

Table 5.1 Number of patients' data analysed per week of training

Week	Number of COPD Subjects	Number of Control Subjects
1	68	22
2	65	22
3	64	22
4	63	22
5	62	22
6	59	22
7	59	22
8	59	21

Trajectory of RT

Figure 5.1 shows the training progression in total work performed averaged over weeks one to eight in both groups. Healthy controls performed RT at significantly higher workloads than patients with COPD at all time points ($p \leq 0.05$). This division between controls and COPD patients remained throughout.

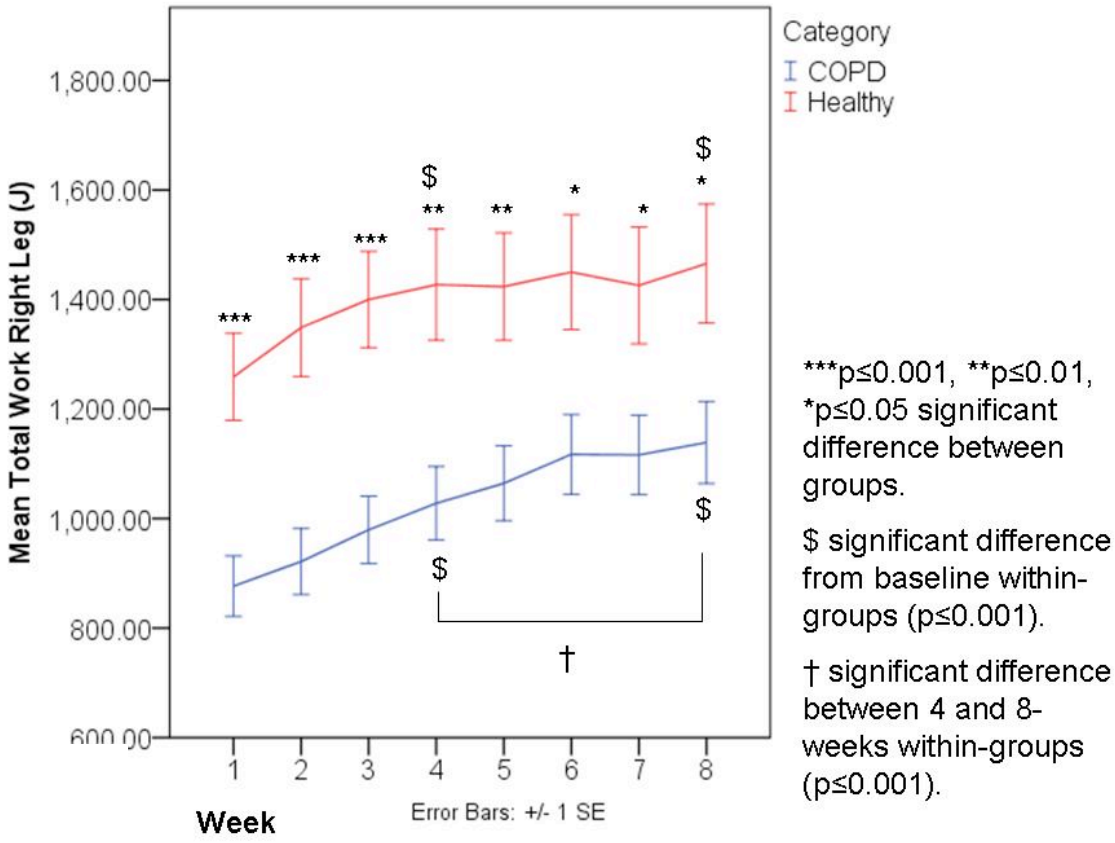


Figure 5.1 Training intensity progression of total work performed at weeks one to eight in patients with COPD and healthy controls

Both groups had significant within-group improvements in work performed at four and 8-weeks compared to baseline. Workload improvement plateaued in the healthy control group after 4-weeks (no significant improvement between weeks 4-8). However COPD subjects continued to have significant improvements in training workload between four and 8-weeks (p≤0.001). GEE analysis found that the gradient of the slopes were not significantly different from one another in statistical terms (p=0.06), although there was a trend towards significance. Therefore, one can conclude that work load progression was significant within, but not between groups.

Figure 5.2 shows the equivalent figure for the progression in training peak torque over 8-weeks. The trajectory shown is similar to work progression shown in figure 5.1. Again, healthy controls produce higher peak torque values than patients with COPD at all time points (p≤0.05). Both groups displayed significant improvements in peak torque performed at four and 8-weeks compared to baseline. Peak torque improvement plateaued in the healthy control group after 4-weeks (no significant improvement between weeks 4-8). However COPD subjects continued to have significant improvements in peak torque between four and 8-weeks (p≤0.001).

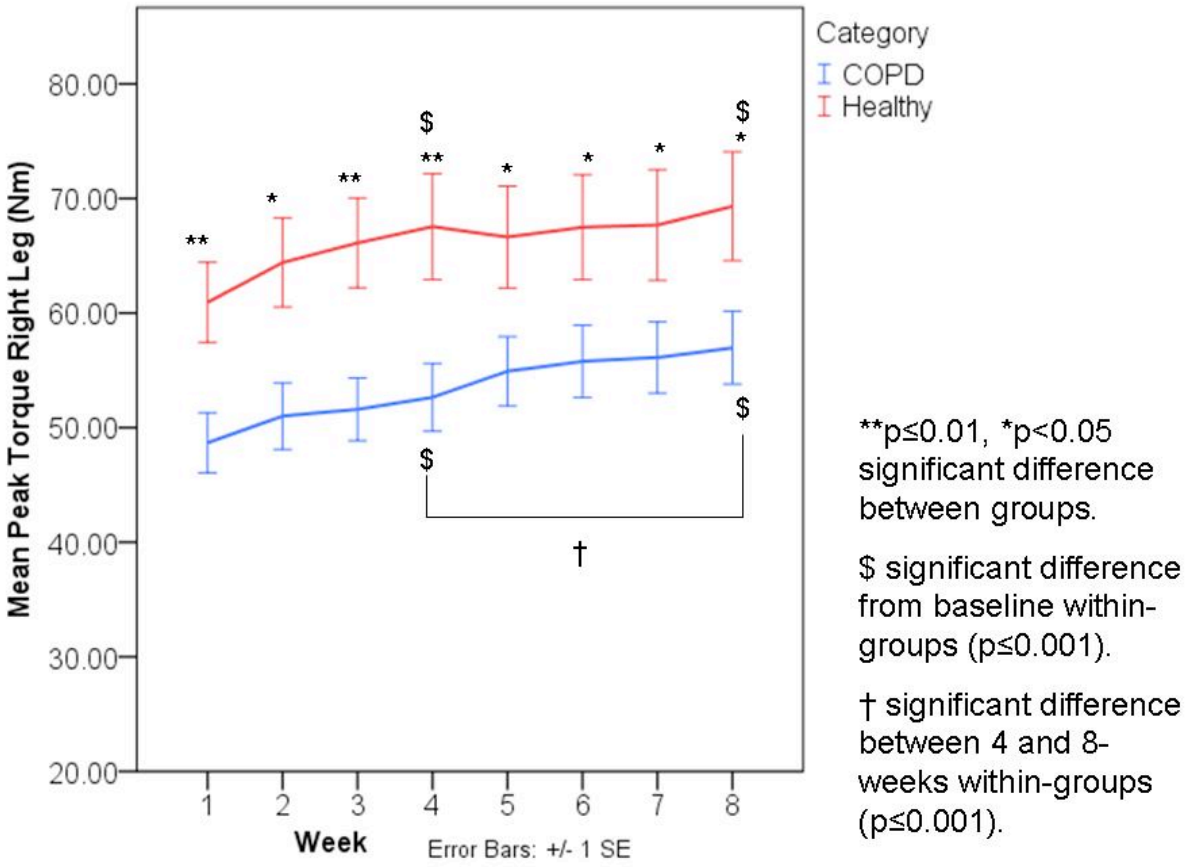


Figure 5.2 Training intensity progression of peak torque performed at weeks one to eight in patients with COPD and healthy controls

GEE analysis revealed that the progression slopes for patients and controls were not significantly different to each other ($p>0.05$). Again the rate of torque progression was significant within, but not between groups.

Table 5.2 shows the mean percentage change in isokinetic training work and torque from baseline at four and 8-weeks, in patients and controls.

Table 5.2 Mean percentage change in isokinetic total work and peak torque during the 8-week resistance training programme, in patients with COPD and healthy controls

Values are mean (SD)	**COPD Subjects**	**Healthy Controls**
Percentage change in work weeks 1-4	20.4 (27.2)	11.7 (16.8)
Percentage change in work weeks 1-8	32.4 (32.8)	12.3 (15.5) *
Percentage change in torque weeks 1-4	10.0 (20.4)	8.7 (12.2)
Percentage change in torque weeks 1-8	19.0 (25.4)	12.3 (15.5)

*** $p<0.05$ between group difference**

The results indicate that the majority of the progression in training work and torque occurs within the first 4-weeks, for both groups. The percentage changes in isokinetic work exceeded changes in torque at both time points for patients with COPD. For healthy controls this was only the case for weeks 1-4. There was a statistically significant between-group difference for the percentage change in isokinetic work in weeks 1-8 (12.3% for controls, 32.4% for patients with COPD, $p<0.05$).

Fatigue Profile

Figure 5.3 shows the plot of FI for isokinetic work, averaged each week for the 8-week training programme.

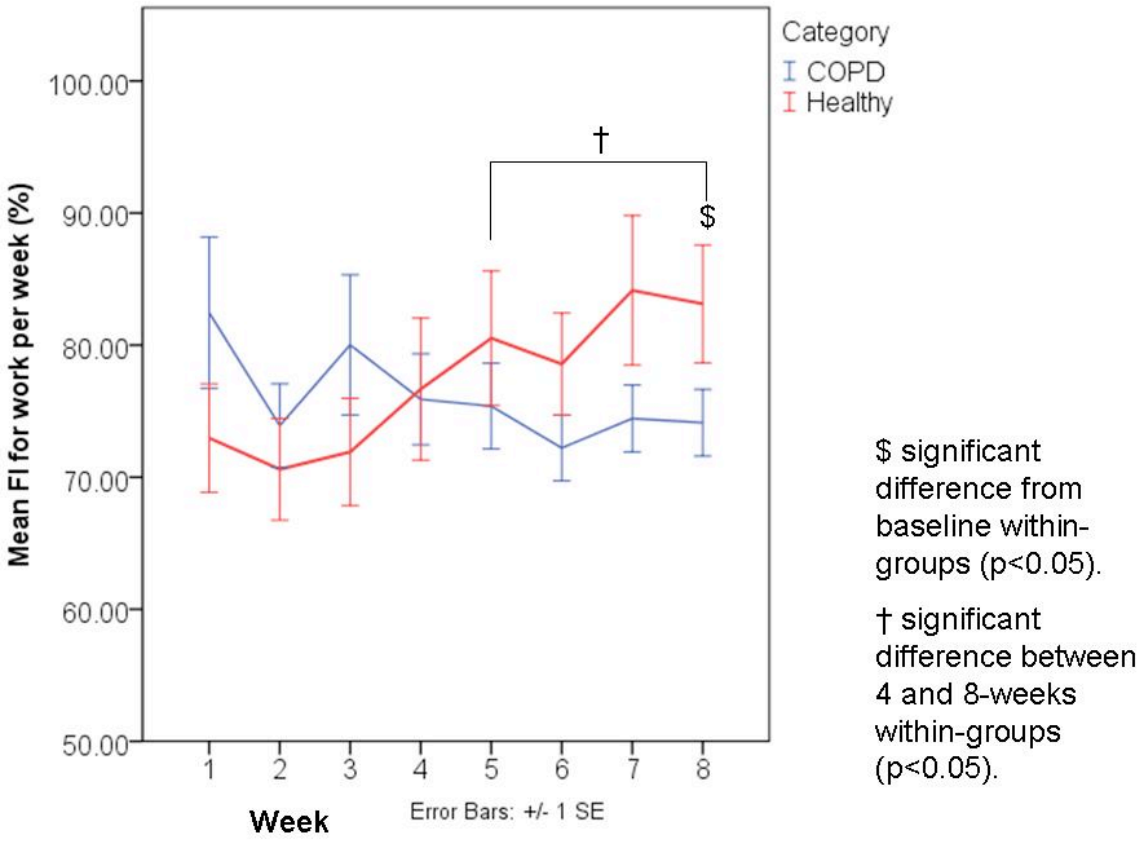


Figure 5.3 Mean fatigue index (FI) for work over 8-weeks in patients with COPD and healthy controls

There were no significant differences between the two groups, at any time point for FI. However there was a trend towards a difference between the groups at weeks one (patients have a higher FI) and seven [controls have a higher FI (both p=0.06)]. A high FI indicates high fatigue resistance (FR), i.e. an increased ability to sustain muscular contraction/ lower fatigue rate. Interestingly, the groups appear to cross over at week four. Prior to this, patients have a greater FI and are therefore more fatigue resistant compared to controls. By the end of the 8-week programme, controls appear to develop FR, whilst patients with COPD do not. To put this into context, figure 5.4 shows the absolute decay in work (i.e. decline from set 1 to set 5), averaged per week.

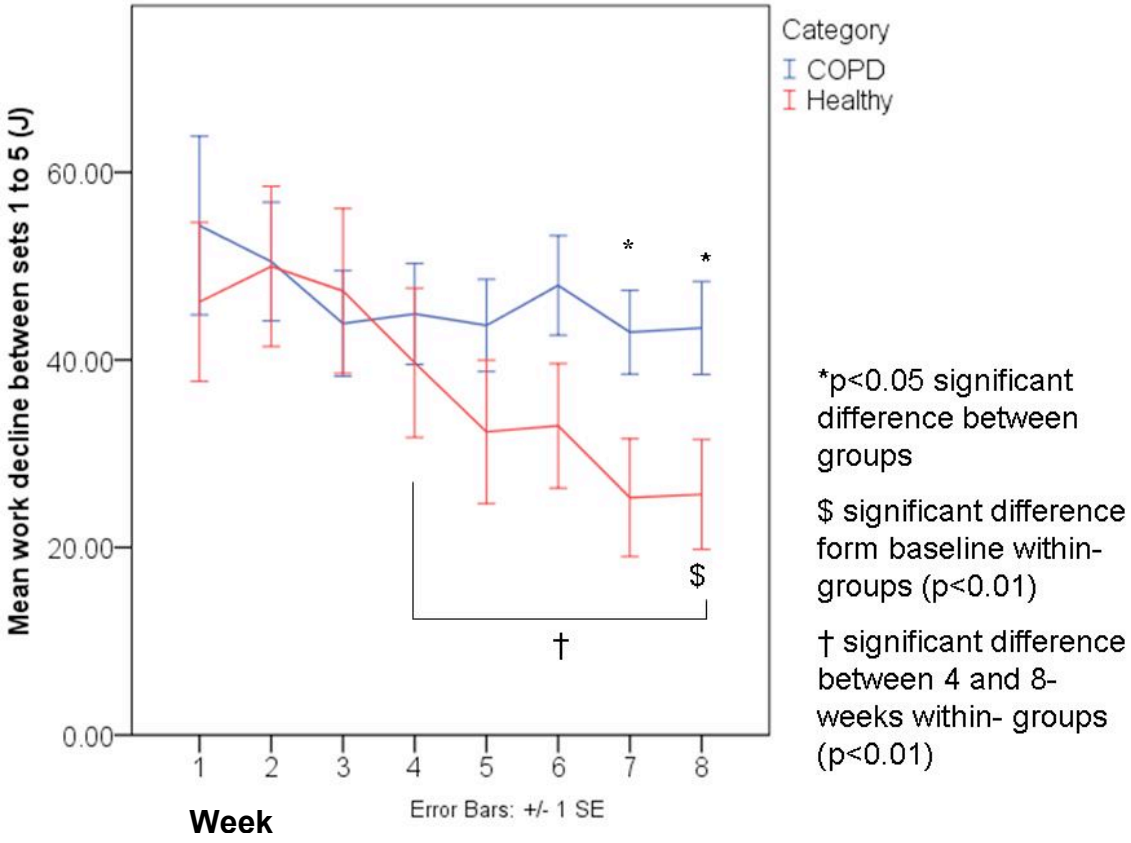


Figure 5.4 Absolute decline in isokinetic work between sets 1 to 5 averaged per week in patients with COPD and healthy controls

The absolute decline in work is comparable between the two groups for weeks one to six. However healthy controls were performing at consistently higher training work loads than patients with COPD during these RT sessions (see figure 5.2). There is a significant difference between groups for work load decline at weeks seven and eight ($p<0.05$) as healthy controls became more fatigue resistant. The work load decline was significantly reduced for controls at 4-weeks [mean decline (±1SE) 35.0 (30.8) J] and 8-weeks [22.7 (23.3) J], compared to baseline [40.4 (33.0) J; both $p<0.01$].

For patients with COPD the absolute decline in work does not dramatically reduce, [mean change in work decay (±1SE) from baseline to 8-weeks -8.6 (7.1) J- figure 5.4] and their FI is lower (figure 5.3- at 4 and 8-weeks compared to baseline). These observations were not statistically significant, compared to baseline within the COPD group. However, patients were producing progressively higher workloads compared to baseline over the 8-week period, where as there was a plateau in the performance of control subjects at 4-weeks (figure 5.1).

Figure 5.5 presents the FI for isokinetic torque, averaged each week for the 8-week training programme.

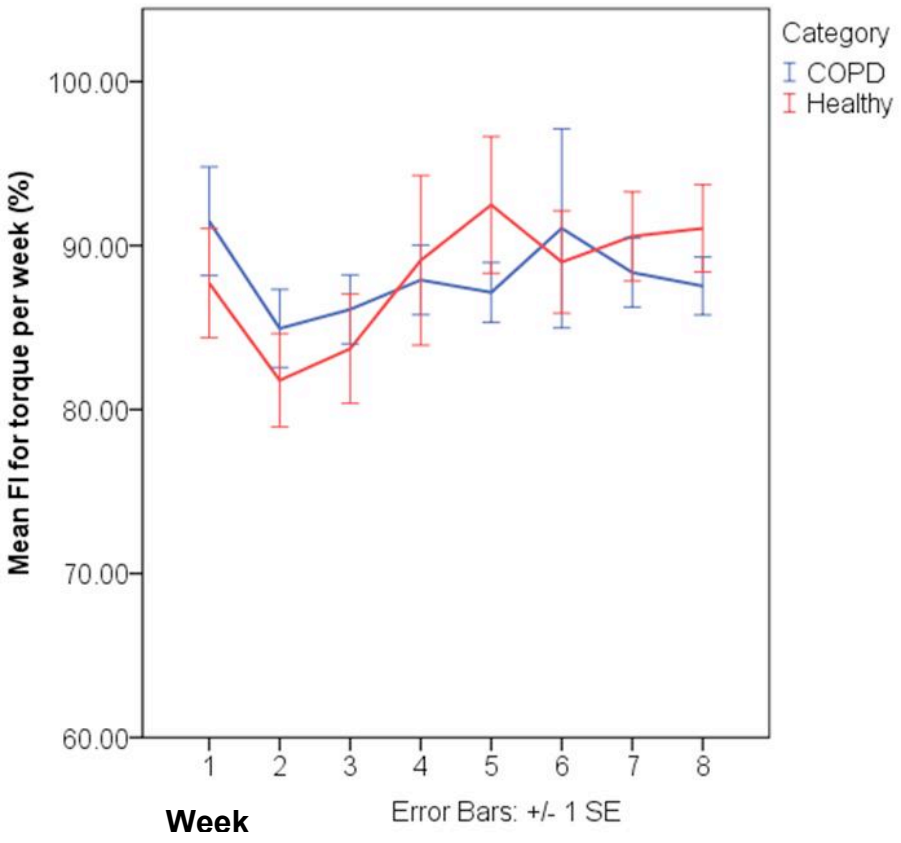


Figure 5.5 Mean fatigue index (FI) for torque over 8-weeks in patients with COPD and healthy controls

There were no significant differences between or within-groups for torque FI over time [(all p>0.05) figure 5.5]. The FI for torque remained at approximately 90% for both groups over 8-weeks. This is in contrast to the FI for work which was lower and showed definite changes over the 8-week training period.

Figure 5.6 shows the absolute decline in torque between sets 1 to 5, averaged each week for both groups. There were no significant differences for the average torque decay between groups, at any time point (all p>0.05).

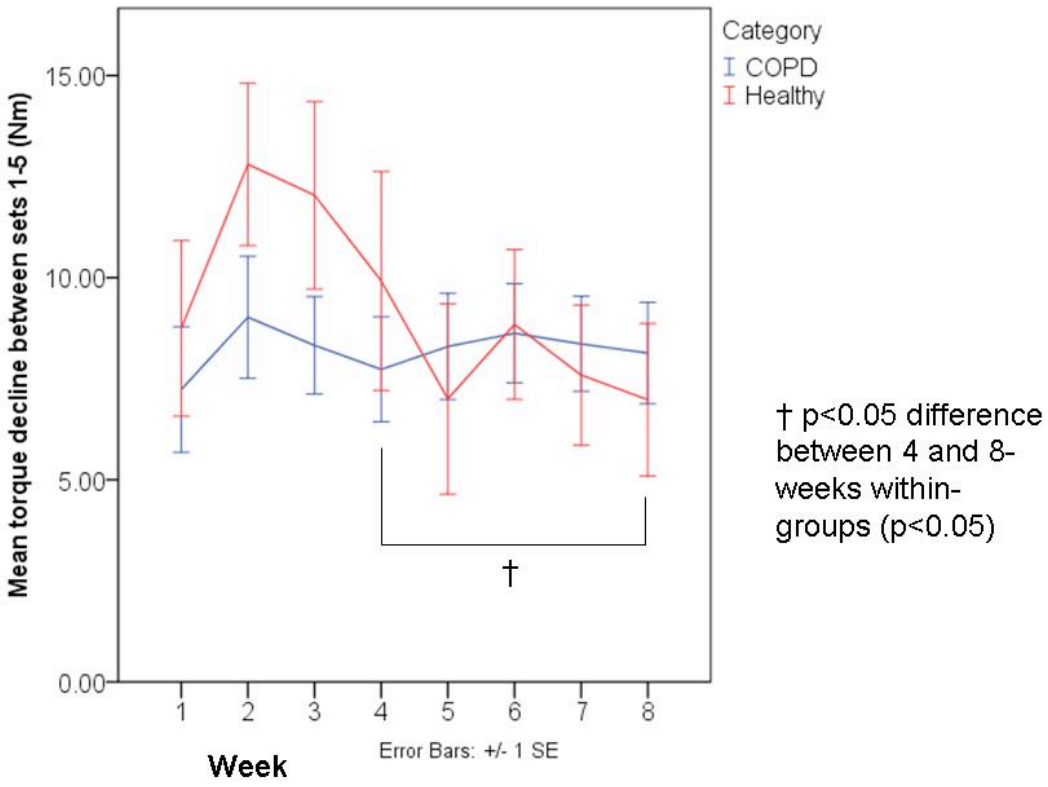


Figure 5.6 Absolute decline in isokinetic torque between sets 1 to 5 averaged per week in patients with COPD and healthy controls

Within-group changes in torque decline were only significant for control subjects between weeks 4 to 8 when the average decline was reduced by -2.4

(1.7 SE) Nm ($p<0.05$). The change in torque decline for patients with COPD was minimal and actually increased slightly between weeks 1 to 8 by 1.6 (1.3 SE) Nm.

Relationship between training intensity and changes in outcome measures

Mean values and percentage change from baseline are shown in table 5.3 for the outcome measures: isometric strength, isokinetic strength (at 60°/sec) and thigh lean mass, which were measured before and after four, and 8-weeks of RT. Controls were significantly stronger than patients with COPD at baseline for both isometric and isokinetic strength ($p<0.05$). Both groups made significant improvements in all outcomes at four and 8-weeks, compared to baseline.

Table 5.3 shows that the greatest proportion of the improvements occurred within the first four weeks of RT for both groups. There were no statistically significant differences between groups for the changes at 4 or 8-weeks. Both groups made significant within-group changes from baseline at weeks 4 and 8. The only significant improvement between weeks four and eight was for thigh mass in healthy controls ($p\leq0.05$). Percentage changes in the measures of strength exceeded changes in thigh mass in both groups at 4 and 8-weeks. Patients with COPD had larger percentage improvements in quadriceps strength (isometric and isokinetic) compared to healthy controls, at weeks four and eight; although this did not reach statistical significance.

Table 5.3 Mean values and percentage change from baseline for isometric strength, isokinetic strength (at 60°/sec) and thigh lean mass, at 4 and 8-weeks in patients with COPD and healthy controls

	Baseline	Week 4	Week 8
COPD Subjects			
Isometric Quadriceps Strength (Nm)			
Mean (SD)	110.4 (45.8)	126.1 (50.5)***	129.6 (53.0)***
Mean % change from baseline (95% CI)	----------	16.6 (11.5 – 21.7)	18.7 (13.7 – 23.7)
Isokinetic Quadriceps Strength (Nm)			
Mean (SD)	79.1 (34.7)	99.9 (58.0)***	97.8 (41.7)***
Mean % change from baseline (95% CI)	----------	32.7 (20.3 – 45.0)	30.6 (20.6 – 40.6)
Thigh Lean Mass (g)			
Mean (SD)	3919.8 (1005.2)	4089.7 (1092.9)***	4157.1 (1128.1)***
Mean % change from baseline (95% CI)	----------	4.5 (2.9 – 6.1)	5.4 (3.6 – 7.2)
Healthy Control Subjects			
Isometric Quadriceps Strength (Nm)			
Mean (SD)	137.7 (43.8) †	151.8 (57.1)**	155.0 (59.1)**
Mean % change from baseline (95% CI)	----------	9.8 (1.1 – 18.5)	12.0 (3.4 – 20.5)
Isokinetic Quadriceps Strength (Nm)			
Mean (SD)	99.7 (36.3) †	113.7 (44.5)**	113.1 (45.7)**
Mean % change from baseline (95% CI)	----------	15.0 (5.8 – 24.1)	13.5 (4.1 – 23.0)
Thigh Lean Mass (g)			
Mean (SD)	4224.6 (862.2)	4387.9 (919.0)***	4440.0 (954.7)***$
Mean % change from baseline (95% CI)	----------	4.1 (2.3 – 6.0)	5.5 (3.6 – 7.3)

***p≤0.001, **p≤0.01 within-group change from baseline,

$ p≤0.05 within-group change weeks 4-8.

† p<0.05 difference between groups at respective time point.

The intensity of isokinetic work and torque (from figures 5.1 and 5.2), over the 8-week training period were correlated with changes in the outcome measures shown in table 5.1. For isokinetic training work (180°/sec), there were only significant associations with isokinetic peak torque (60°/sec: r=0.48, p=0.000, figure 5.7) in patients with COPD and with isometric strength for healthy controls (r=0.55, p=0.012, figure 5.8). These were positive correlations. i.e. greater training work progression was associated with larger improvements in static and dynamic measures of strength.

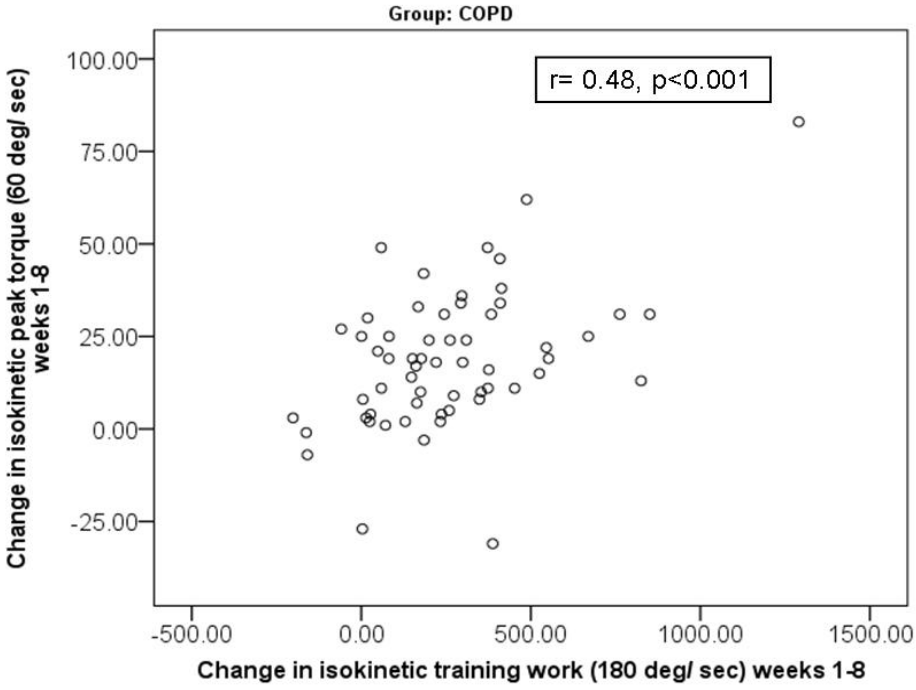


Figure 5.7 Scatterplot to show the relationship between training work intensity and changes in isokinetic peak torque between baseline and 8-weeks in patients with COPD

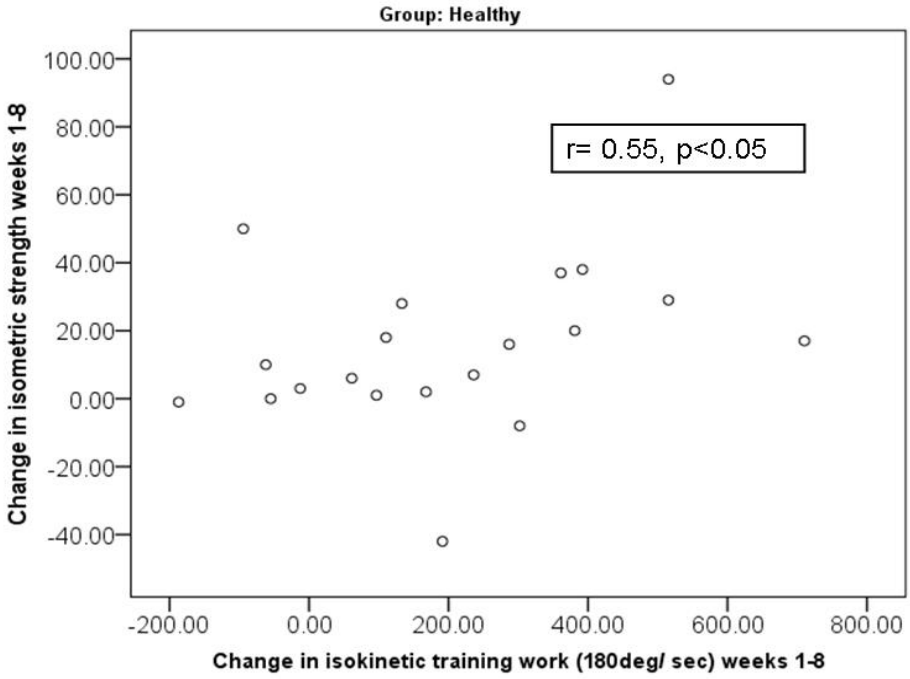


Figure 5.8 Scatterplot to show the relationship between training work intensity and changes in isometric strength between baseline and 8-weeks in healthy controls

For patients with COPD, there were some weak and moderate correlations between training torque changes (180°/sec) and isometric strength (r=0.33, p=0.012), as well as isokinetic peak torque (60°/sec: r=0.61, p=0.002, figure 5.9). Again these were positive correlations. There were no statistically significant correlations between changes in training torque and the outcome measures, at 8-weeks, for healthy controls.

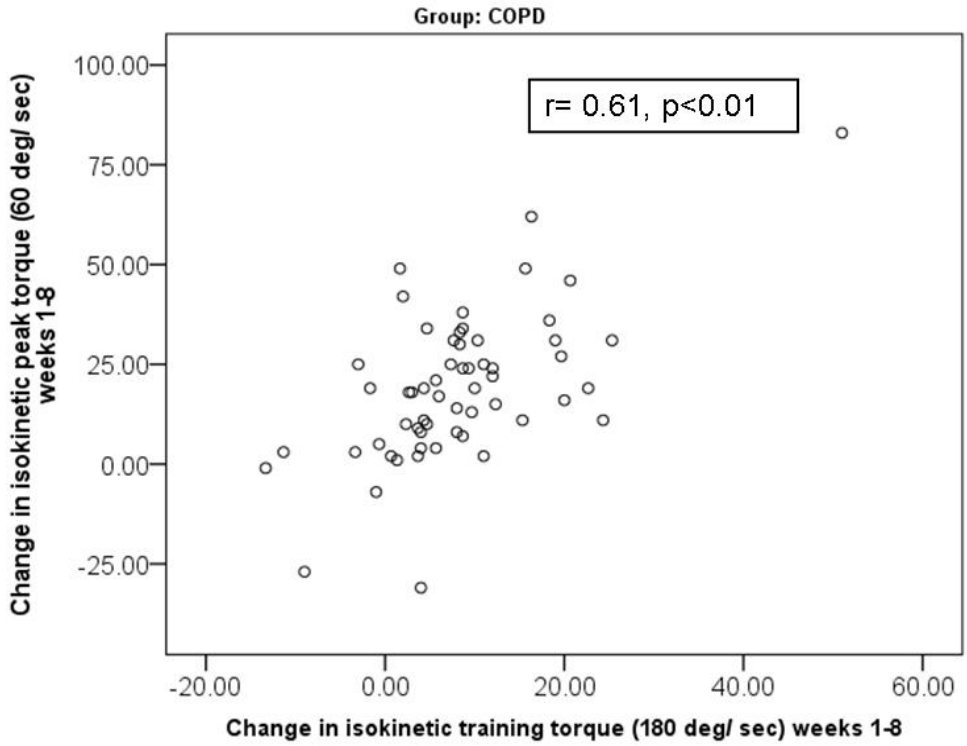


Figure 5.9 Scatterplot to show the relationship between training torque intensity and changes in isokinetic peak torque between baseline and 8-weeks in patients with COPD

A clear outlier is identified in figures 5.7 and 5.9. Data entry was checked and this was deemed to be a genuine, valid response. Therefore the outlier has remained in the figures. However, with the outlier removed the r value in figure 5.7 reduces to 0.33 ($p<0.05$) and 0.48 ($p<0.01$) in figure 5.9. Changes in thigh

mass were not correlated with either measure of training progression (work or torque), in both groups.

The cardio-respiratory load and symptoms associated with the RT programme are explored in chapter 6.

5.6 Discussion

The aim of this chapter was to precisely explore the training intensity trajectory and fatigue profile of an isokinetic RT programme, observing the variables of work and peak torque. Another objective was to analyse the relationship between RT intensity and changes in outcome measures at four and 8-weeks. This is important as the relationship between RT intensity and outcome measures, such as strength has been poorly described in the COPD population. This is the first study to explore these factors in such detail serially during an 8-week training programme, in patients with COPD. Furthermore the results have been compared to a healthy age-matched control group, training at the same time; this again is novel.

The results in this chapter and also in chapter 4 suggest that COPD patients, who are exercising at lower absolute workloads compared to healthy controls, can make comparable gains in muscle strength and mass. Controls subjects were performing the RT programme at higher absolute intensities for both isokinetic work and torque at weeks 1 to 8; compared to COPD subjects. There were significant improvements within both groups for training intensity progression, in terms of both work and peak torque at week 8 compared to

week 1. Control subjects appeared to show a plateau in their rate of training progression after 4-weeks for both work and peak torque. Subjects with COPD however continued to demonstrate significant improvements in training intensity progression beyond 4-weeks. Despite this, there were no statistically significant differences between the two groups for training intensity progression. Indeed, the gradient of the training intensity slopes were similar for both work and torque in both groups (GEE analysis $p>0.05$). One may speculate that, if training were to continue in the COPD group, they too would eventually demonstrate a plateau in performance and may even reach the levels of normal subjects.

Despite lower absolute values for isokinetic work and torque in patients compared to controls during RT; COPD subjects had greater percentage improvements in work and peak torque (relative to their baseline), when compared to healthy controls at 4 and 8-weeks. This was statistically significant between the groups for changes in training work progression (weeks 1-8). Moreover, percentage improvements in isokinetic training work exceeded changes in peak torque for both groups. This suggests that Isokinetic work may be a more sensitive measure to change after RT, than peak torque. This highlights the importance of measuring work which is cumulative rather than merely reporting peak torque (maximal force), as significant improvements may be missed.

In addition, isokinetic work as an output appears to be more susceptible or sensitive to muscle fatigue compared to peak torque. The data in the current

chapter shows that the FI for peak torque did not really change over the 8-week training period and remained at around 90% in both groups. The absolute decay in peak torque (from set 1 to set 5) also showed only minimal change over the 8-week training programme. It could be that because peak torque represents maximal strength, it may not be likely to change by a large magnitude on a session by session basis. In contrast, the fatigue profile for isokinetic work demonstrated definite changes during the RT course. Healthy controls experienced less fatigue in isokinetic work production as the RT programme progressed. This is evident due to an increased FI (significant between weeks 4-8) and a significant reduction in the absolute work decline (from set 1 to set 5) in this group at weeks 4 and 8 compared to baseline. The FI improved by around 10% from week 1 to week 8 and the reduction in absolute work decline was an average of 20 Joules by week 8 compared to week 1 of RT. In other words, healthy controls were able to demonstrate better fatigue resistance and experienced less fatigue as the RT programme progressed. These findings are comparable to others who have shown that RT can improve FR (Campos et al. 2002;Izquierdo et al. 2006;Kemmler et al. 2004;Salvador et al. 2009). These changes were not apparent in the COPD group as their resistance to fatigue did not improve with training for both work and torque.

Whilst one would expect subjects with COPD to fatigue to a greater extent (and more rapidly) than healthy controls (Allaire et al. 2004;Swallow et al. 2007a), it remains unknown why the elderly control group in the current study would develop a resistance to muscle fatigue after RT, whilst the COPD group

did not. This is a novel finding. In the only previous study to evaluate the FI after training in patients with COPD, the authors did see a significant improvement in FR after NMES (Neder et al. 2002). However it is difficult to compare the findings in this study to the current study because the RT modalities were different and the knee extensor testing velocity was slower in the NMES study (PAV of 70°/ sec). Although muscle fatigue, and particularly the FI, is seldom reported in studies of patients with COPD we do have some data from healthy individuals to which we can compare the results of the current study. In a study of healthy elderly subjects, who underwent the same RT protocol as described in this thesis, subjects demonstrated an average percentage decline of 22% in sets 2-5 compared to set 1, during a single testing session (Rawson 2010).The healthy control group in the current study had a fall in fatigue index of approximately 28% at the start of the training programme (100%: no fatigue, minus 72%: FI in week 1). The study by Salvador and colleagues examined the percentage change in FI after an 8-week RT programme in healthy young subjects. The change in FI was -17% in men and -31% in women, using the alternative FI were a lower score is better. Unfortunately we do not know what would constitute a clinically significant improvement in FI and this makes the interpretation of the findings difficult. One may hypothesize that because control subjects showed a plateau in their progression of training work and torque (after 4 weeks), that they merely became more efficient at performing the same 5 sets of 30 repetitions task each session. i.e. they were not producing any greater force in the last few weeks but their decay in force was reduced. Were as, the patients with COPD continued to increase their isokinetic training work and torque output beyond

4-weeks. Therefore these subjects were producing greater muscle force (in terms of torque and work) but as consequence, displayed greater fatigue (lower FI and greater absolute decline in work and torque between sets 1 to 5, as training progressed). Because of skeletal muscle dysfunction in patients with COPD, changes in muscle function and FR may take longer to occur. One could imagine that had the RT programme continued beyond 8-weeks, subjects with COPD may have also reached a plateau in training progression and therefore may have shown reductions in fatigue. These speculations are supported, to a certain extent, by literature in healthy subjects which suggests that muscle fatigue is related to production of greater peak muscle force initially (Pincivero, Gandaio, & Ito 2003), as the FI is a ratio based on the initial force generated. Therefore men are more likely to display greater fatigue than women because their initial force is superior (Pincivero, Gandaio, & Ito 2003). Correspondingly, if patients with COPD were producing greater isokinetic work and torque values (in relative terms: % improvement from their baseline) than healthy controls towards the end of the 8-week programme; then one may expect their level of fatigue to be greater. Furthermore, we know that fatigue in itself has a positive effect on strength as an outcome measure (Abdalla, McGregor, & Strutton 2007;Izquierdo et al. 2006). Therefore if patients with COPD displayed more fatigue during training, this may account for their continued progression in training-related strength outputs. It is perhaps a limitation that the responses were not compared in male and female participants.

If we consider that the decline in muscle function seen with normal ageing might be more pronounced or accelerated in patients with COPD, this may also account for some of the differences in the fatigue profile of the two groups. We are aware from the literature, that there is some debate as to whether older people are more or less fatigue resistant, compared to younger subjects. One argument is that older people are more fatigue resistant than the young because ageing muscle relays more heavily on oxidative rather than glycoltic pathways and therefore lactate production is reduced (Lanza, Russ, & Kent-Braun 2004). A recent study by Rawson et al. analysed the fatigue for old (mean age 66 years) and young healthy men using the same isokinetic RT protocol described in this thesis (Rawson 2010). This protocol took place on one testing session. The authors of this study concluded that older men demonstrated enhanced FR during their chosen testing protocol and commented that this type of testing favours the oxidative preferences of ageing muscle, as intermittent contractions favour the replenishment of oxygen within the muscle. However, we know that patients with COPD who have skeletal muscle dysfunction have reduced oxidative capacity within the muscles. This is because of a relative reduction in the proportion of type I (oxidative) fibres and an increased proportion of type IIb (glycolytic) fibres, as well as a lower fibre-to-capillary ratio and reduced oxidative enzymes (Allaire et al. 2004;Hurley et al. 1986;Whittom et al. 1998). Therefore the patients with COPD in the current study may have been lacking the capacity within the muscles to replenish oxygen during the RT programme. One may wonder weather healthy controls were able to do this, as their muscles have the usual oxidative preferences seen in normal elderly muscle and whether this

accounts for their reduced fatigue evident over the training period. It is likely that if the training programme variables were altered; such as contraction speed, number of repetitions and rest intervals, that this would have influenced FR. For instance we recognise that elderly subjects experience more fatigue than younger people when the speed of contraction is at a high PAV, but not at slower speeds or during static contractions (Callahan & Kent-Braun 2011). It is also apparent that isometric testing is better at evoking fatigue than isokinetic testing in healthy subjects (Corin, Strutton, & McGregor 2005). We do not know if the same is true in subjects with COPD because the current study did not investigate fatigue during the isometric quadriceps testing. The aim of this chapter was to explore fatigue over the time course of a RT programme, rather than to observe fatigue during a single assessment. In future, one may wish to explore which types of training and assessment protocols are the best at evoking fatigue in patients with COPD.

Data in chapter 4 demonstrated that the RT programme led significant within-group improvements in quadriceps strength, thigh lean mass and whole-body exercise performance in all groups, regardless of supplementation. In this chapter the outcomes of muscle strength (isometric and isokinetic: 60°/sec) and thigh lean mass have been further explored by observing an interim measurement after 4-weeks of RT. The data shows that both groups made significant within-group improvements in all outcomes and there were no significant differences between the groups. The greatest proportion of the improvements occurred within the first four weeks both groups, in all outcomes. This is in line with the training intensity information as most of the

progression in work and torque occurred in the first four weeks; controls plateau after this point in terms of training progression. Again it is clear that there was a transfer effect from training because peak torque improved at a speed below (60°/sec) the training velocity (180°/sec) and isometric strength also improved. Also, improvements in isokinetic strength measures again exceeded static measures, in both groups at 4 and 8-weeks. There were some associations between training intensity (work/ torque) and the measures of isometric and isokinetic strength (60°/sec) after 8-weeks in both groups. These were positive, suggesting that increased training intensity leads to improved gains in muscle strength which are 'dose-dependant.' Also the association between peak torque progression in training was greater with isokinetic rather than isometric strength and probably reflects the specific adaptation to the training which was also isokinetic.

In addition we can once more observe this disconnect between the changes in muscle mass, which are much lower than changes in muscle strength for both groups. These findings replicate what is reported in previous literature (Jones et al. 2004). One might have expected that the muscle mass changes would not be apparent until the 8-week measure, as muscle hypertrophy (change in fibre/ muscle group size) is known to occur later as a result of long-term training (Sale 1988). However, in the current study, there was a significant increase in muscle mass by week 4; at which point the majority of the improvement had occurred. Between baseline and week 4, thigh lean mass improved by 4.5% in patients with COPD and by 4.1% for healthy controls (both $p \leq 0.001$). Between weeks 4 and 8, thigh lean mass only

increased by a further 0.9% in patients and 1.4% in controls ($p<0.95$ between week 4 and 8 in controls only). This is unusual as mass changes generally occur later and most likely dispels the theory put forward in chapter 4, that changes in thigh mass may have been greater if the RT were to continue beyond 8-weeks. Interestingly changes in muscle mass showed no correlation with RT intensity.

In this chapter, limits were set to be able to present the information coherently. For instance, by reporting the right leg only and by observing the averages per training week. This may be a limitation as important within-session and between leg variations could have been overlooked. However the results for the left leg are reported in appendix 13 and mirror the findings from the right leg. The progression in work and torque training output, were similar for both legs. Furthermore, it may have been appropriate to assess the outcome measures at further time points throughout the RT programme. Important adaptations may have occurred prior to the 4-week assessment and serial measures each week would have been preferred. However, this was not undertaken due to time constraints for the assessor and concerns about fatigue in the individuals undergoing RT, as extra assessments could theoretically negatively influence training output.

In conclusion, this is the first study to precisely explore training intensity progression and fatigue/ force decay during a RT programme in patients with COPD, and to compare the results with a healthy control group. The isokinetic

RT programme chosen provided a unique opportunity to explore these factors in detail by measuring both isokinetic work and peak torque.
The data shows that, whilst patients with COPD perform RT at much lower absolute intensities (compared to healthy controls), they can still make comparable improvements in muscle strength and mass. Both groups were able to significantly improve training intensity for both work and torque over the 8-week training period. The trajectory of progression was similar in both groups.

Fatigue is rarely reported in COPD literature and when it is, the term has been defined in various ways. To my knowledge, only one previous study has examined how fatigue changes after training in patients with COPD, this was following 6-weeks of NMES training (Neder et al. 2002). Clinicians do not have an MCID value established for FI changes and therefore we do not know what would represent a clinically significant improvement in FI. These factors create a challenge when interpreting the results. The current study has revealed that healthy controls became more FR (display less fatigue) over 8-weeks with the chosen RT protocol. However subjects with COPD did not. Further study is required to explore fatigue in more detail in subjects with COPD, by altering training and assessment variables (including isometric protocols) to establish which are the best to evoke fatigue.

The work presented in this chapter implies that isokinetic work is a more sensitive measure to change following RT, compared to peak torque.. This highlights the importance of measuring work than merely reporting peak

torque as significant improvements may be missed. Work was also found to be more sensitive to fatigue. The fatigue characteristics of isokinetic work remain largely unknown in healthy and diseased populations as peak torque is normally just reported. Future research should continue to explore work as an outcome, alongside peak torque, as the two variables provide different information.

Chapter 6

Cardio-respiratory load imposed by the resistance training programme

6.1 Introduction

Chapter 4 reported the main outcomes from the RCT of RT and protein supplementation given at the time of training. As protein did not enhance the benefits of RT, the COPD sub-groups are pooled in this chapter. Interestingly, one of the findings of chapter 4 was that the RT programme led to appreciable improvements in whole-body exercise performance, assessed using cycle ergometry. This suggests some functional carry over of the benefits of RT and may indicate central adaptations to training. This chapter aims to describe the ventilatory load imposed by the chosen RT programme and the symptomatic response to training. The data presented compares the responses in patients with COPD, to healthy age-matched controls. This data compliments chapter 5 by analysing a further component of the RT programme.

In addition to the improvements in muscle mass and strength derived from RT; this type of training may also offer advantages for patients with severe COPD, where ventilatory limitation is often the main contributor to exercise intolerance (O'Donnell 2001). There is a school of thought, that for more disabled patients with COPD; RT of small muscle volumes may allow for higher training intensities at a muscle level compared to whole-body exercise.

Theoretically, RT should not activate the cardiopulmonary system to the same extent as whole-body exercise (Simpson et al. 1992). Probst and co-workers have shown that cardiopulmonary stress is lower during RT when compared to endurance training at the start, middle and end of a 12-week training programme (Probst et al. 2006). This was observed in both objective (e.g. minute ventilation, oxygen uptake derived from a portable breath by breath system) and subjective (i.e. symptom scores) parameters. More recently, Sillen *et al* found that the metabolic response was significantly lower still with NMES compared to RT during a single session (Sillen et al. 2008). However, the authors concluded that both NMES and RT resulting in acceptable metabolic responses and symptom scores for patients (Sillen et al. 2008).

Whilst the two afore mentioned studies have measured the cardio-respiratory response to conventional quadriceps RT (multigym, isotonic training), the response has not been explored for isokinetic training. The isokinetic RT protocol described in this thesis utilised a training velocity of 180°/sec. This PAV represents the middle of the spectrum of speeds available on isokinetic machines and, as such, represents the centre of the muscular strength to endurance continuum (Kraemer et al. 2000). We know from chapters 4 and 5 that this type of training can significantly improve muscle strength and thigh mass. However one may also speculate that this type of training activates the cardio-pulmonary system, as changes in whole-body exercise performance have also been noted (chapter 4).

6.2 Aims

Two aims were formulated to assess and compare the cardio-respiratory load imposed by the RT programme in patients with COPD and healthy age-matched controls.

1. To assess the breath-by-breath response to one RT session in a convenience sample of subjects by measuring parameters of ventilation and gas exchange (compared to a maximal CPET at baseline).

2. To observe symptom scores (Borg) and physiological variables (HR and SpO_2) in response to RT during the 8-week training period.

6.3 Methods

The methodology for the RCT discussed in this thesis is described in detail in chapter 3. This includes recruitment of subjects, details of the intervention and outcome measures assessed. Chapter 4 outlines the main outcomes of the RCT. As protein supplementation did not have augment the effects of RT, the results presented in this chapter are pooled for supplemented and placebo COPD groups.

Breath-by-breath sub-group analysis

A convenience sample of 14 patients [mean (SD) age 70.8 (7.9) years, FEV_1 1.2 (0.2) l, 7 male] and 11 healthy controls [age 65.6 (6.0) years, FEV_1 2.5 (0.9) l, 3 male] underwent breath-by-breath analysis of their ventilation and

gas exchange during one of their RT sessions (5 sets of 30 maximal knee extensions). Subjects wore a mouth piece attached to the same ergospirometry system used for the CPET (figure 6.1), as described in chapter 3. This analysis took place between training sessions 8-12 (range) and the five training sets on the right leg were chosen for analysis. The recorded outcomes were: peak oxygen uptake (VO_2: mls/kg/min) and minute ventilation (VE: l/ min) for each individual, on each of the 5 RT sets. These values were compared to the baseline CPET (cycle ergometry) values.

Figure 6.1 Breath-by-breath analysis of ventilation and gas exchange during one resistance training session, using the ergospirometry system

Symptomatic response to RT

Perceptions of breathlessness (score 0-10) and RPE (score 6-20) were measured using Borg scales (Borg 1982) throughout the entire 8-week training programme in all subjects (see chapter 5 for the number of subjects

analysed per week). Other physiological responses (HR and SpO_2) were also recorded before training and after each training session. Patients were asked to rate their Borg scores based on how they felt at 'peak' exercise. These values were averaged each week (i.e. training sessions 1, 2 and 3= week 1 etc).

6.4 Statistical analysis

Breath-by-breath sub-group analysis

The ventilation outcomes (VO_2 and VE achieved) during the single RT session are presented as a percentage of the maximal CPET at baseline. Actual values achieved during each set are also reported. Independent and paired t-tests were used to look at differences between and within groups, respectively.

Symptomatic response to RT

Symptom scores were averaged for weeks one, four and eight of training. A repeated measures ANOVA was performed to analyse within and between-group changes in these outcomes between weeks 1, 4 and 8.

6.5 Results

Breath-by-breath sub-group analysis

Table 6.1 shows the mean (±SD) percentage of VO_2 (mls/ kg/ min) and VE (l/ min) achieved on each set, during a single RT session, in patients and healthy controls. These values are presented as a percentage of the maximum

achieved on the baseline cycle ergometry test (CPET), described in chapter 3. In COPD subjects, the percentage of VO_2 and VE increased with each set (from 49.1 to 60.1%: VO_2 and from 57.6 to 72.2%: VE). The VO_2 increase was significant between sets 1 and 2 [49.1 to 54.8% ($p<0.05$)]. Controls worked at the highest percentage of their VO_2 and VE on set 3 (52.3%: VO_2, 65.3%: VE), values were reduced in sets 4 and 5. Overall, COPD subjects worked at higher percentages of their maximal VO_2 and VE compared to controls during all 5 sets; although this wasn't statistically significant.

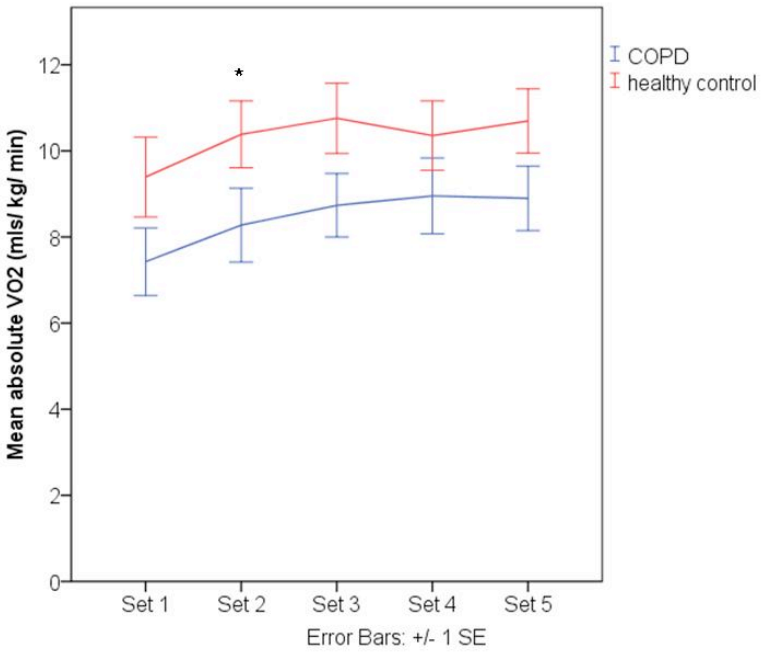
Table 6.1 The percentage of maximum VO_2 and VE achieved for sets 1-5, during one RT session, compared to maximal cycle ergometry testing at baseline

Values are mean (± SD)	**COPD Subjects (n=14)**	**Healthy Controls (n=11)**
%VO_2 achieved set 1	49.1 (16.3)	45.7 (15.3)
%VO_2 achieved set 2	54.8 (16.9)*	50.4 (13.9)
%VO_2 achieved set 3	58.9 (17.6)	52.2 (14.3)
%VO_2 achieved set 4	60.0 (17.9)	50.4 (14.3)
%VO_2 achieved set 5	60.1 (17.7)	51.4 (10.5)
%VE achieved set 1	57.6 (16.7)	49.8 (17.7)
%VE achieved set 2	66.1 (19.2)	62.1 (15.7)
%VE achieved set 3	70.3 (17.3)	65.3 (17.7)
%VE achieved set 4	71.6 (19.9)	62.6 (15.7)
%VE achieved set 5	72.2 (20.5)	63.6 (17.7)

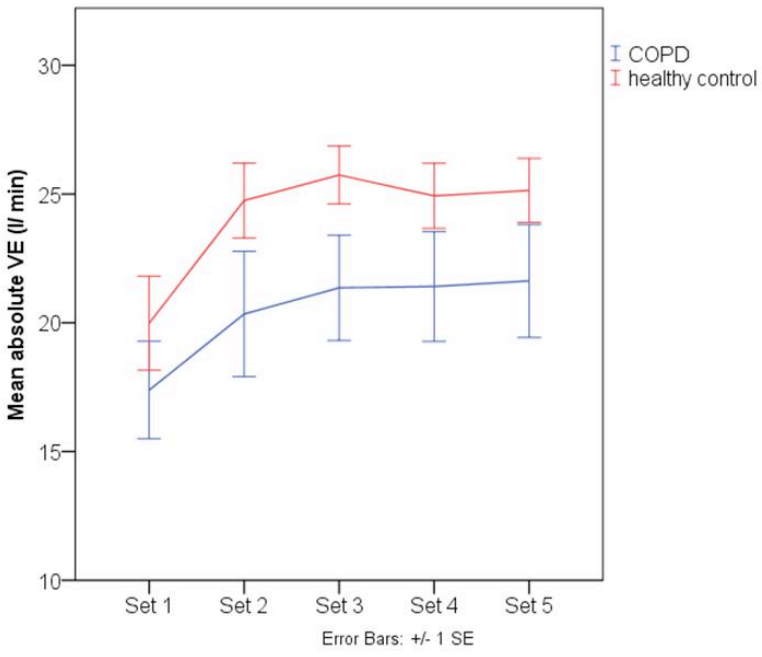
*** $p< 0.05$ between sets 1 and 2 for % VO_2 achieved in patients with COPD**

Figures 6.2 A and B show the actual VO_2 and VE values achieved on each set, in both groups. The difference between groups was only significant for

VO_2 on set 2 ($p<0.05$), where the value was significantly higher for control subjects.



A. *p<0.05 significant difference between groups



B.

Figure 6.2A and B Mean actual VO_2 (A) and VE (B) achieved during sets 1 to 5 of a single resistance training session in patients with COPD and healthy controls

Controls achieved an average quadriceps work load over these five training sets of 1032.6 J compared to 750.9 J in patients. This difference was statistically significant ($p<0.05$).

Chapter 4 reports the CPET outcomes after the RT intervention; there were significant improvements in CPET work and some ventilation parameters after RT for whole groups (of COPD patients and controls). CPET changes in this subgroup of 14 patients and 11 controls were significant for peak work [mean change (±SD) 8.5 (7.9) W for patients and 8.5 (6.2) W for controls, both $p<0.05$], but not for ventilation/ gas exchange parameters.

Symptomatic response to RT

Symptom scores (Borg breathlessness and RPE) were recorded immediately before and after each training session, as were measures of HR and SpO_2 in both groups. Table 6.2 shows the average values of these parameters in weeks one (sessions 1-3), four (sessions 10-12) and eight (sessions 22-24) in both groups.

The results in table 6.2 indicate some significant differences in symptom and physiological variables between patients with COPD and healthy controls. Borg breathlessness scores were higher in patients with COPD, before and after exercise, at all time points ($p\leq0.01$ compared to controls). Resting HR was higher in patients with COPD compared to controls at all time points ($p\leq0.05$). As expected, SpO_2 values were significantly lower in patients compared to controls, before and after RT at weeks one, four and eight

(p≤0.05). There was no de-saturation in SpO_2 evident during RT for subjects with COPD. However those on LTOT had already been excluded from the study. SpO_2 actually improved in the COPD group after training compared to baseline, in week one (≤0.001).

Table 6.2 Symptom scores and physiological parameters before and after resistance training in weeks 1, 4 and 8 for patients with COPD and healthy controls

Values are mean (±SD)	**COPD Subjects**	**Healthy Controls**	**Significant difference between groups**
Week 1: Start of training			
Pre Borg	0.5 (0.8)	0.0 (0.0)	p≤0.001
Post Borg	3.0 (1.7) $	1.8 (1.1) $	p≤0.01
Pre RPE	6.0 (0)	6.0 (0)	NS
Post RPE	14.3 (1.9) $	14.2 (2.6) $	NS
Pre SpO_2 (%)	94.0 (4.2)	96.3 (1.5)	p≤0.05
Post SpO_2 (%)	94.6 (4.3) $	96.8 (1.0)	p≤0.05
Pre HR	81.8 (11.8)	72.7 (11.2)	p≤0.01
Post HR	98.3 (14.7) $	95.4 (13.4) $	NS
Week 4: Mid-point			
Pre Borg	0.7 (0.8)	0.0 (0.0)	p≤0.001
Post Borg	3.2 (1.7) $ †	2.0 (1.3) $	p≤0.01
Pre RPE	6.0 (0)	6.0 (0)	NS
Post RPE	13.9 (2.1) $	13.9 (2.6) $	NS
Pre SpO_2 (%)	94.3 (4.4)	96.7 (0.8)	p≤0.05
Post SpO_2 (%)	94.6 (4.4)	96.7 (1.2)	p≤0.05
Pre HR	84.1 (11.6) †	75.1 (9.5)	p≤0.001
Post HR	100.9 (16.2) $	97.4 (14.5) $	NS

Continues overleaf (week 8 results)

Table 6.2 continued

Week 8: End of training			
Pre Borg	0.6 (0.8)	0.0 (0.0)	p≤0.001
Post Borg	2.9 (1.4) $	1.6 (1.3) $	p≤0.001
Pre RPE	6.0 (0)	6.0 (0)	NS
Post RPE	13.4 (2.1) $ †	12.8 (2.9) $	NS
Pre SpO_2 (%)	94.4 (4.5)	96.9 (1.3)	p≤0.05
Post SpO_2 (%)	95.2 (2.1)	96.7 (1.0)	p≤0.05
Pre HR	82.5 (12.5)	76.5 (9.9) †	p≤0.05
Post HR	100.1 (15.6) $	97.7 (15.4) $	NS

NS not significant; $ p≤0.001 significant within-session (pre to post) change within-group; † p≤0.05 significant within-group change compared to week 1; ≠ p≤0.05 significant within-group change compared to week 4.

Borg breathlessness and RPE scores increased after RT, at all time points. These changes were significant in both groups (p≤0.001). Post-RPE (after RT) was lower in week eight compared to week one for patients with COPD (p≤0.05).

The RT programme caused significant increases in heart rate (compared to pre training), each week for both groups (p≤0.001).

6.6 Discussion

The aim of this chapter was to describe the cardio-respiratory load imposed by the RT programme used in the RCT, described in this thesis. Typically RT is not thought to activate the cardio-respiratory system to the same extent as

endurance training. However the changes in whole-body exercise performance, ventilation and gas exchanges variables, evident in chapter 4, imply that the RT protocol was able to sufficiently activate these central systems.

The data in the current chapter supports this notion that the RT protocol was able to sufficiently activate the cardiopulmonary system and may be responsible for central adaptations to training.

Typically, COPD patients were working at higher percentages of their peak VO_2 and VE (in relation to their maximal baseline CPET) compared to healthy controls during the assessment of ventilation and gas exchange during a single RT session. However this did not reach statistical significance probably due to the low sample size (type II error). Controls were working at higher actual VO_2 and VE levels and were producing more quadriceps isokinetic work than COPD patients for each of the five RT sets ($p<0.05$ between groups).

Two previous studies have examined the cardio-respiratory response to RT. The study by Sillen and colleagues compared quadriceps RT [3 x 8 repetitions (70% of 1RM) to NMES and also evaluated their results in comparison to a maximal CPET (Sillen et al. 2008). This allows for easy comparison to the current study. Peak VO_2 (% of maximum from CPET) was 57% after RT and 34% after NMES ($p<0.001$ between RT and NMES). These findings are strikingly similar to the current study were the percentage of maximum VO_2

ranged from 49.1% to 60.1% after RT, in patients with COPD. Peak VE (% max voluntary ventilation) was also comparable after RT in both the study by Sillen *et al* [58% (Sillen et al. 2008)] and in the current study were the range was 57.6% to 72.2% for patients with COPD.

The second study by Probst and co-workers (Probst et al. 2006) is difficult to compare to the current study as the ventilation data is reported over a 12-week training period rather than a single session. Furthermore, the results are presented as actual values rather than related to a percentage of maximum. Actual values for VE (l/min) after leg press exercise ranged from 22 (week one) to 26 (week 12). These findings are similar to the current study as patients with COPD had actual VE values of approximately 21 l/min after sets 3-5 of RT.

There were limitations with the sub-group breath-by-breath analysis presented; primarily that the sample size was too small to detect significant differences between the groups. Also, the ventilatory requirements of this training protocol were not directly compared to different modes of exercise. For instance, it would be interesting to see where this novel RT regime sits on the spectrum between typical endurance (e.g. walking) and RT (e.g. 3 sets of 8 repetitions at 70% of 1 RM). In addition; although ventilatory and gas exchange measurements were taken at a standardised training session number (8-12 out of 24 total sessions), it may have been interesting to take serial measures over the 8-week training period and to re-calibrate from a new CPET, besides baseline. This would allow one to observe if the ventilatory

load of the training changed in both groups, during the 8-week training period. Finally, measures of lactate would have been of interest to compliment the results and one could have tracked the recovery of ventilatory parameters if the device had remained on the subject during the recovery period.

Thinking about the symptoms associated with the RT programme, the data shows that the training was well tolerated in both groups. The maximum Borg breathlessness score after RT for patients was 3.2 (moderate) at week 4 and RPE was highest at week one (14.3). There were no significant differences between patients and controls for Borg scores after RT, therefore patients with COPD did not perceive the training to be any harder than healthy controls. However, control subjects were performing the RT at a much higher intensity (see chapter 5). There is some evidence to suggest that patients with COPD become desensitised to the perception of training intensity as their reported RPE at week 8 was 13.4. This is significantly lower than at week one (14.3). Borg scores after RT in the study by Sillen *et al* (Sillen et al. 2008) were similar to the current study, 3 for breathlessness and 3 for RPE (using the modified 0-10 Borg scale). What was not measured was the motivation for the exercise session and post-training enjoyment or satisfaction which can be measured using questionnaires. This is perhaps a limitation, as motivation can have a bearing upon effort and ultimately the outcomes of training (Seynnes et al. 2004). Therefore these unmeasured (confounding) factors may impact upon outcomes in chapters 4, 5 and 6. However, one assumes that a persons' motivation is reflected in their effort during training. This was 'somewhat hard' to 'hard', on average, in the patients with COPD using the Borg RPE scale. It

may be interesting in future to observe the training progression and outcome responses in those patients with a lower perceived effort.

There was no evidence of oxygen de-saturation after RT in the current study; however those on LTOT had already been excluded from the study. There were significant HR changes after training in both patients and healthy controls, for weeks 1, 4 and 8. If we consider that subjects with COPD had a mean HR after training of around 100 bpm, this relates to 66% of their maximum heart rate [220 minus mean age of the group (68 years)]. Using the same formula, control subjects were working at 63% of their maximum heart rate. A HR of 65 to 85% of maximum relates to the target training zone for cardio-respiratory fitness and fat burning (Tanaka, Monahan, & Seals 2001); therefore training at this level can be expected to bring about central adaptations. Subjects in the study by Probst and co-workers also had a HR approaching 100 bpm after leg press exercise [99, 99, 104 at weeks 1, 6 and 12 respectively (Probst et al. 2006)]. However the HR changes after RT were significantly lower than walking, cycling (week 1 and 6 only) stair climbing and arm cranking.

In conclusion, the data outlined in this chapter shows that the RT protocol was able to sufficiently activate the cardiopulmonary system; this was evident by subjects working at high proportions of their maximum VO_2, VE and HR. This may explain the significant changes in whole-body exercise performance, reported in chapter 4, which would be typically seen with traditional endurance training. This was in addition to bringing about changes in quadriceps muscle

strength and mass (chapter 4). The chosen RT programme was performed comfortably by patients as Borg breathlessness scores remained at an acceptably low level after training and no oxygen de-saturation occurred. Whilst it may be that in the most severe patients, we can not overcome ventilatory limits; this RT protocol offers an attractive alternative training option. As the RT programme was able to influence both strength and endurance outcome measures (chapter 4) it is likely that the protocol sits fairly centrally on the continuum between resistance and endurance training.

Chapter 7

Reliability properties of the ActiTrac® accelerometers and changes in physical activity after resistance training

7.1 Introduction

This chapter describes a pilot study to assess the test re-test reliability, reproducibility and sensitivity of the ActiTrac® activity monitors to establish their suitability for use in patients with COPD. Previous work in healthy subjects has shown that these monitors are reliable when compared to indirect calorimetry (Welk, Almeida, & Morss 2003). It was important to identify whether these monitors were reliable and sensitive enough to detect different speeds of walking prior to their use in patients with COPD for the main RCT. This is particularly important for slow speeds of walking, typical of patients with COPD. Therefore the monitors were tested in a healthy individual (author) in a pilot study, prior to their use in patients.

A secondary aim of this chapter was to explore whether RT led to changes in physical activity (PA), as detected by the ActiTrac® monitors and a none disease-specific questionnaire in patients with COPD. As protein did not enhance the benefits of RT (see chapter 4), the COPD sub-groups are pooled in this chapter.

Levels of physical activity (PA) are known to be reduced in patients with COPD, when compared to healthy age-matched subjects (Pitta, Troosters,

Spruit, Probst, Decramer, & Gosselink 2005). Reduced PA in patients with COPD is associated with a poor prognosis and an increased risk of hospitalisation (Garcia-Aymerich et al. 2006). One of the aims of Pulmonary Rehabilitation (PR) is to improve physical functioning and to increase domestic activity in patients with COPD (Hunter et al. 2006).The objective monitoring of physical activity in COPD is therefore of clinical interest, particularly when we aim to measure changes in PA in response to rehabilitation programmes. Several studies have explored changes in PA after PR (Troosters et al. 2010) and there is huge variation in the improvements reported. This probably reflects heterogeneity in the PR programmes and devices used to collect PA data. The percentage change in PA after rehabilitation ranged from 0 (Steele et al. 2008) to 70 % (de Blok et al. 2006). This review highlighted that changes in PA after PR are not guaranteed. We also know that PA is only marginally correlated with the degree of airflow obstruction in this population, indicating that other factors may be involved, such as peripheral muscle weakness (Garcia-Aymerich et al. 2006).

One of the objectives of this thesis is to explore the role of RT (in isolation, i.e. outside of the context of conventional PR), upon physical performance in patients with COPD. RT would be expected to increase muscle mass and strength. However the translation of improvements in strength to daily PA is inconclusive (O'Shea et al. 2009). Clearly, for increases in strength and mass to be meaningful, they must translate into functional benefits for patients. Intuitively, one might expect that if you can improve muscle strength then daily

activities may be easier to perform and, as a consequence, PA would increase.

Traditionally, PA has been derived from questionnaires, interviews and more recently accelerometers (Pitta et al. 2006b). In this thesis, three measures of PA are explored: the ActiTrac® accelerometer, the adapted PA questionnaire for the elderly (baseline only) and the DASI.

7.2 Aims

There were two primary aims in this chapter; to evaluate the reliability properties of the ActiTrac® accelerometers, prior to their use in patients with COPD and to assess changes in PA after RT.

ActiTrac® pilot study

The aims of this pilot study were to assess the ActiTrac® activity monitors for:

1. Test re-test reliability of each monitor over five tests, at a given speed
2. Between monitor reproducibility at a given speed
3. The ability to discriminate between different speeds of walking

This was performed in a healthy individual (the author), prior to their use in patients with COPD.

Change in PA after RT

Three aims were formulated:

1. To describe PA levels at baseline, comparing patients with COPD to healthy age-matched controls using the adapted PA questionnaire for the elderly
2. To assess whether PA levels improved after RT in a sub-group of patients with COPD, using an accelerometer and the DASI
3. To observe the relationship between predicted VO_2 max from the DASI and measured peak VO_2 from cycle ergometry after RT.

7.3 Methods

ActiTrac® pilot study

The ActiTrac® activity monitor (IM Systems, Baltimore, USA) is a lightweight device (34g) and has a biaxial accelerometer with sensitivity to detect movement as slight as 0.012g. The intensity of activity is expressed in reference scale data counts of 0-250 (acceleration per unit time). The device is simple to use, with no power buttons. There is a 'mark' button on the monitors if one wants to indicate specific bursts of activity. The ActiTrac® software is used to initialise the monitors and download data. The monitors are relatively inexpensive (approximate cost: device £530, software £260); particularly in comparison to other devices on the market (discussed in chapter 2, section 2.6.3 *Physical activity*).

Before each session the activity monitors are initialised (labelled and clock set) via the computer interface so that subsequent activities can be recognised. All monitors were initialised at x1 sensitivity, with one minute

epochs (number of data points per hour); this was chosen based upon manufacturer's guidelines. No feedback is given to the wearer of the monitor. The monitors were labelled on the outside with numbers 1-5. At different times, five different monitors were attached to a waist belt on the right hip of a healthy subject (LH, author- figure 7.1) who performed five; 20-minute walks at three different speeds in five minute sections. These walks were performed in a random order.

Figure 7.1 ActiTrac® monitor placement

The walking course was a standard 10m shuttle walk test [SWT (Singh et al. 1992)] area on a hard, flat surface. Three speeds of the endurance shuttle walk test [ESWT (Revill et al. 1999)] were chosen and these constant speeds were determined by audio signal [1.78 kilometres per hour (kph) = slow, 3.6kph= moderate, 5.54kph= fast]. The mark button was pressed at the start and end of each 5-minute walking period.

Average activity counts (acceleration per minute), for each five minute bout were extracted for analysis using the ActiTrac® software [version 8.5.5: IM Systems, Baltimore (MA) USA- example of screenshot figure 7.2]. The range of these counts is from 0-250 acceleration counts per minute. Data can also be expressed as milli-g acceleration units.

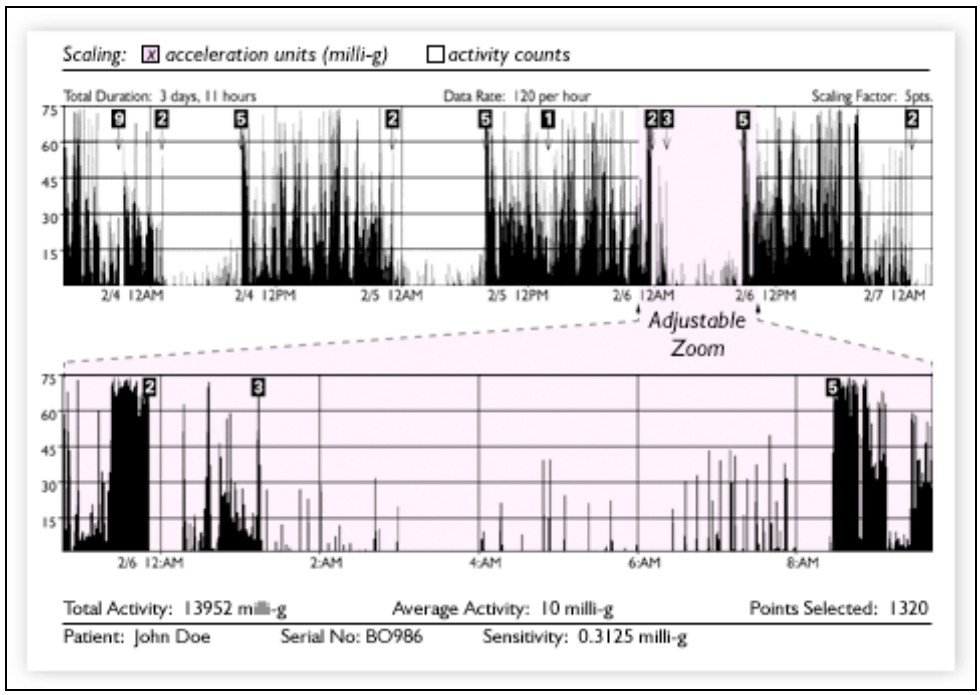


Figure 7.2 Example of screenshot from the ActiTrac® software

Change in PA after RT

At baseline only, the adapted PA questionnaire for the elderly (Voorrips et al. 1991) was completed by both groups. This questionnaire is not disease-specific and was chosen to allow comparison between patients with COPD and healthy controls. The questionnaire has previously been used to describe patients with COPD (Engelen et al. 2000;Serres et al. 1998). The questionnaire is interviewer-led and asks about household sporting and leisure activities within the last year, to produce an overall activity score of 0-

35. A higher score indicates a greater level of PA. The researcher is responsible for giving an intensity code for each of the sporting and leisure activities. This code is based on the energetic costs of activities [originally based on the activity questionnaire described by Baecke and co-workers (Baecke, Burema, & Frijters 1982)]. Test-retest reliability, and validity of the modified questionnaire, compared to 2 independent methods of assessing physical activity (pedometer and 24hour activity recall) in the elderly have been established (Voorrips et al. 1991). A copy of the questionnaire and scoring system is shown in appendix 14.

PA was measured in a subgroup of 20 patients with COPD before and after the RT programme using the ActiTrac® accelerometer and the DASI. The ActiTrac® was given to the wearer subject for 7 days before and 7 days after training. Subjects wore the same monitor number pre and post-RT, as the monitors were found to not be interchangeable (see pilot study results). Prior to each seven day monitoring period, the activity monitors were initialised (labelled and clock set) via the computer interface. All monitors were initialised at x1 sensitivity, with one minute epochs; as described above. Patients were asked to wear the monitors for a 12-hour period each day (e.g. 9am to 9pm). Patients received no feedback from the monitors. Average activity counts were reported (0-250 acceleration counts per minute range). The mean acceleration per minute was averaged over 7 days. Compliance with the monitor was assessed with a home recording diary (see appendix 15).

The DASI was also completed by this subgroup (see appendix 16). The DASI asks individuals whether or not they can perform 12 activities at that moment in time and was therefore used to determine if changes in PA occurred during the intervention period. Additionally, from the DASI, VO_2 max (mls/ /kg/ min) can be estimated using the following equation:

$$V0_2 \text{ max} = 0.43 \text{ X DASI} + 9.6$$

The DASI (Hlatky et al. 1989) was developed in a cardiac population and has good correlation with peak oxygen uptake (r= 0.80). It's utility and relationship to oxygen uptake in patients with COPD is unknown. The relationship between VO_2 max estimates from the DASI and peak VO_2 from the incremental cycle ergometry test at 8-weeks were therefore compared.

Changes in muscle strength, mass and whole-body exercise performance are also reported for the sub-group of 20 subjects to aid comparison between the functional outcome measures.

7.4 Statistical Analysis

ActiTrac® pilot study

As the data was not normally distributed, non-parametric statistical tests were utilised. Descriptive statistics are presented to display within-monitor variation over the five tests, at three different speeds [mean ± SD, 95% CI, median with IQR and the coefficient of variation (CV)]. The CV is a measure of the relative

variation of distribution, independent of the units of measurement. It is calculated by dividing the standard deviation by the mean and is expressed as a percentage. The non-parametric Kruskal-Wallis test (with post-Hoc Mann-Whitney U tests) was used to assess between monitor reproducibility and to see if all monitors could distinguish between the three speeds of walking.

Change in PA after RT

An independent t-test was used to compare the two groups for baseline PA levels using the adapted PA questionnaire for the elderly. Paired t-tests evaluated changes in PA from the ActiTrac® and DASI, within the COPD sub-group. Furthermore the changes in muscle strength, mass and whole-body exercise performance (peak work) are reported for the sub-group of 20 subjects with COPD. Again within-group changes were assessed using a paired t-test. The effect size for changes in PA after the intervention was calculated by dividing the mean difference by the standard deviation of the pre-intervention measurement. By calculating effect sizes, the magnitude of change can be judged using the following criteria: small; 0.2 to 0.5, moderate; 0.5 to 0.8 and large; >0.8 (Cohen 1988).

To explore the relationship between VO_2 estimates from the DASI and the cycle ergometry test, at 8-weeks, Pearson's correlation coefficient was calculated. The strength of any associations is as described in chapter 5 (i.e. weak/ moderate/ strong). Also, the difference between the two VO_2 values derived was compared with an independent t-test.

7.5 Results

ActiTrac® pilot study

Table 7.1 shows descriptive statistics and within-monitor variation over the 5 tests. Monitor 1 had the worst reproducibility. In general, standard deviation (SD) and interquartile range (IQR) increased as speed increased.

Table 7.1 Descriptive statistics and within-monitor variation for the ActiTrac®

		Average activity counts (acceleration/minute)			
Monitor	**Speed**	**Mean (SD)**	**95%CI**	**Median (IQR)**	**CV**
1	**Slow**	41.0 (12.1)	26.0-56.0	39.0 (21.0)	29.5
1	**Moderate**	90.0 (15.7)	70.5-109.5	88.0 (30.0)	17.4
1	**Fast**	128.6 (20.2)	103.6-153.6	121.0 (38.0)	15.7
2	**Slow**	25.4 (2.5)	22.3-28.5	24.0 (5.0)	9.8
2	**Moderate**	46.0 (1.5)	45.0-48.6	47.0 (3.0)	3.3
2	**Fast**	97.0 (4.2)	91.7-102.3	96.0 (8.0)	4.3
3	**Slow**	27.8 (2.4)	24.8-30.8	29.0 (4.0)	8.6
3	**Moderate**	57.2 (3.0)	53.5-60.9	56.0 (5.0)	5.2
3	**Fast**	83.8 (11.9)	69.0-98.6	79.0 (21.0)	14.3
4	**Slow**	24.2 (0.8)	23.2-25.2	24.0 (2.0)	3.3
4	**Moderate**	60.4 (2.9)	56.8-64.0	60.0 (5.0)	4.8
4	**Fast**	97.4 (12.5)	81.8-113.0	95.0 (21.0)	12.8
5	**Slow**	25.0 (3.0)	21.3-28.7	24.0 (5.0)	12.0
5	**Moderate**	59.8 (3.8)	55.1-64.5	60.0 (8.0)	6.4
5	**Fast**	106.4 (12.2)	91.3-121.5	105.0 (22.0)	11.5

Coefficient of variation (CV) was highest for slow speeds in monitors 1, 2 and 5. Kruskal-Wallis analysis indicated that there were significant differences between the five monitors at speeds 1.78km/hr ($p \leq 0.01$), 3.6km/hr and 5.54km/hr (both $p \leq 0.001$). Post-hoc Mann-Whitney tests (with no adjustment for type I errors) revealed that these differences lay between monitor 1 with all other monitors, at each speed. Monitor 1 systematically overestimated and was returned to the manufacturer as faulty. However, there were no significant differences between monitors 2-5, at each speed ($p > 0.05$).

Furthermore, all monitors could distinguish between the 3 speeds of walking [all $p \leq 0.01$ (figure 7.3)].

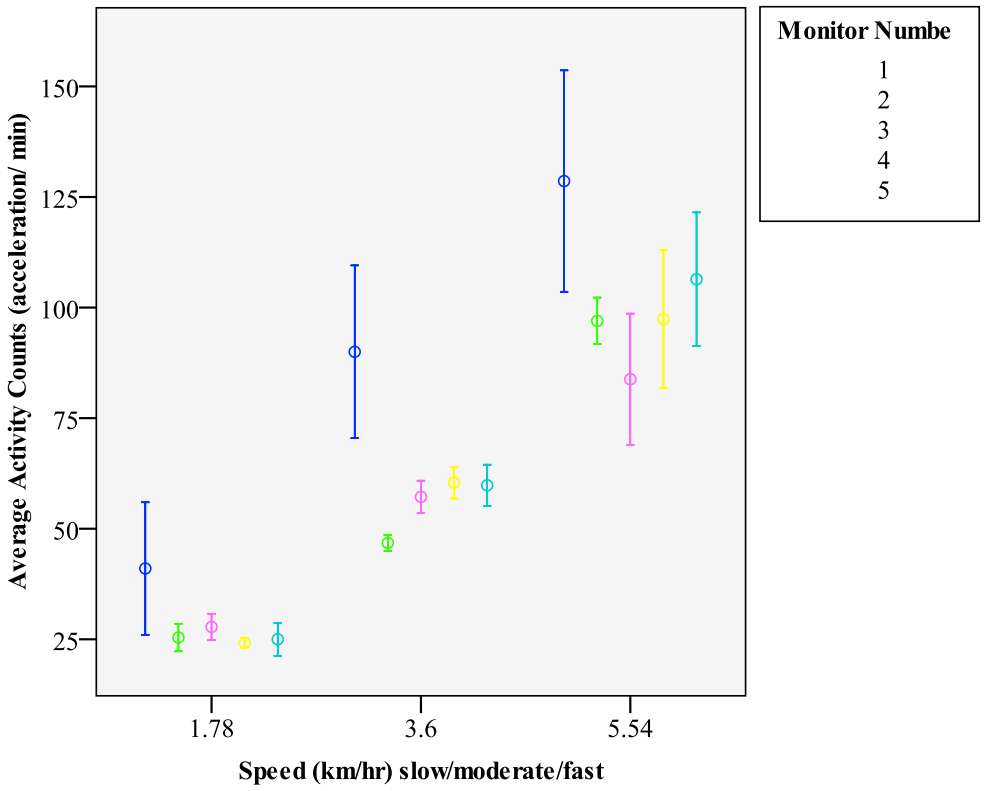


Figure 7.3 Average activity counts by monitor at three walking speeds

Change in PA after RT

Table 7.2 displays the mean scores from the 3 separate domains of the adapted PA questionnaire for the elderly and totals scores, in both healthy controls and patients with COPD, at baseline. Data reflects PA within the previous year and is reported for all subjects who completed a baseline assessment (n= 71 COPD, n= 22 controls). The results in table 7.2 indicate that control subjects were significantly more active than patients with COPD for household, leisure and total scores. However there were no significant differences between the groups for sporting activities.

Table 7.2 Adapted physical activity questionnaire for the elderly: scores for all domains at baseline, in the COPD and healthy control groups

	COPD n=71	Healthy Controls n=22	Between-group significance (p value)
Household	1.4 (0.0)	1.9 (0.0)	0.00
Sport	0.7 (0.3)	1.3 (0.6)	NS
Leisure	4.4 (0.5)	7.2 (1.1)	0.02
Total	6.5 (0.6)	10.3 (1.2)	0.01

Values are mean (±1 SE). NS: not significant

For household activities; control subjects always did light housework (e.g. dusting, washing dishes) in 77.3 % of cases and heavy housework (e.g. washing floors, hovering) in 50.0% of cases. All control subjects prepared their own meals and did their own shopping. Most used a car to go out shopping (63.6%), although 4 subjects used public transport (e.g. the bus) and 4 walked to collect their shopping (18.2% in both cases). Only one control subject did not climb stairs. This was because he lived in a bungalow; he was

physically capable of climbing stairs. Controls climbed stairs more than 10 times a day in just under half of cases (45.8%). Most control subjects did not perform a sport (i.e. a regular commitment or as part of a team) but all had at least one physically active leisure hobby. The top four leisure activities reported by controls were: walking, gardening, dancing and swimming.

5.1% of patients with COPD did not do any light housework and 28.8% never did any heavy housework. 50.8% did their own light housework (± assistance from their spouse). In 10.2% of cases, patients never prepared their own meals and relied upon spouses, family or agencies (e.g. 'Meals on Wheels'). 25.4% of patients with COPD never climbed stairs; although around two thirds of these subjects lived in a bungalow or ground-floor flat. The frequency of stair climbing was less in patients compared to controls; only 8.5% climbed stairs more than 10 times in a day. 5% of patients never went out to do the shopping. In those that did, the car was the preferred means of transport (71.2%). Very few patients walked to collect their shopping (6.8%). No patients with COPD were engaged in regular sport, although five subjects attended a local 'keep fit' class once a week. Patients reported more sedentary hobbies such as knitting, sewing (seated upper limb movements), cooking and painting (standing upper-limb movements). However walking and gardening were the top two leisure activities enjoyed by patients with COPD, as they were in healthy controls. However patients generally scored lower in these activities compared to controls because hours per week and intensity codes were much lower.

Additional PA measures were performed in a convenience sample of 20 patients with COPD, before and after RT. Table 7.3 shows the changes in PA, isometric quadriceps strength, thigh mass and cycling performance after RT for the sub-group. The data in table 7.3 demonstrates that changes in PA were not significantly different than baseline values after 8-weeks of RT, in patients with COPD. There were however statistically significant improvements in the other outcomes (isometric quadriceps strength, thigh mass and cycling performance) after RT. Changes in strength, thigh mass and cycling work supports the findings in chapter 4 for the entire COPD group.

Table 7.3 Changes in physical activity after resistance training in comparison to other outcome measures in a subgroup of 20 patients with COPD

	Baseline	**Week 8**
DASI [mean (SD)]	23.7 (16.4)	24.1 (13.2)
Mean change from baseline (95% CI)	----------	0.4 (-11.2-12.1)
ActiTrac® [mean (SD)] – acceleration/ min	11.4 (9.9)	12.5 (9.9)
Mean change from baseline (95% CI)	----------	1.1 (-3.0-5.2)
Isometric strength [mean (SD)] – Nm	81.3 (28.2)	103.1 (41.9)
Mean change from baseline (95% CI)	----------	21.8 (10.2-33.4)**
Thigh lean mass [mean (SD)] – g	3487.6 (951.2)	3701.7 (949.8)
Mean change from baseline	----------	214.1 (48.2-380.1)*
Peak cycle work [mean (SD)] – W	46.4 (21.4)	59.1 (24.1)
Mean change from baseline (95% CI)	----------	12.8 (3.7-21.9)*

***p<0.05; **p≤0.01 change from baseline**

The effect sizes for the change in DASI score and ActiTrac® counts were very small (0.02 and 0.11 respectively). The effect sizes for quadriceps strength and cycle work were moderate (0.77 strength, 0.60 work). The thigh mass change effect size was small (0.23).

There was a moderate correlation between VO_2 max as calculated by the DASI (19.9ml /kg/ min) and peak VO_2 (16.0mls/ kg/ min) from cycle ergometry ($r=0.59$, $p<0.01$) at week 8. Furthermore, the difference between the peak VO_2 values derived by the two methods was not statistically different.

7.6 Discussion

There were two primary aims in this chapter; to evaluate the reliability properties of the ActiTrac® accelerometers and to assess changes in physical activity after RT.

The results of the pilot study showed that the ActiTrac® activity monitors are reliable in the same wearer, on consecutive occasions. With the exception of monitor 1, there were no significant differences in the average activity recorded by the monitors ($p>0.05$). Therefore the individual characteristics of the activity monitors mean that they are not interchangeable. For this reason, in the study of COPD subjects, all patients were required to wear the same monitor to measure PA at consecutive time points (i.e. pre and post intervention). Also monitor 1 was returned to the company and not used by patients in the RCT.

All monitors could distinguish between slow, moderate and fast speeds of walking. It is important that monitors can detect a range of speeds to accommodate patients with a variety of walking speeds. In particular, the sensitivity to detect slow walking speeds is important for patients with COPD who tend to walk slower than healthy people of the same age due to breathlessness.

This data from the pilot study suggests that the ActiTrac® monitors are reliable, reproducible and that they are sensitive to changes in walking speed. They were therefore deemed to be a feasible, simple to use and relatively inexpensive device; suitable to monitor daily activity in patients with COPD who were engaged in the RCT described in this thesis.

Data in this chapter, confirms that patients with COPD have lower PA levels compared to age-matched healthy controls. This is evident from significantly lower household, leisure and total scores from the adapted PA questionnaire for the elderly, collected at baseline. These findings echo that of several others, as PA is reduced even in those with mild COPD (Pitta, Troosters, Spruit, Probst, Decramer, & Gosselink 2005). The total scores in the current study are similar to those reported by Serres and colleagues: 5 (±1) in COPD subjects and 10 (±2) in control subjects [$p<0.05$ between groups (Serres et al. 1998)]. There were no significant differences between the groups for the sporting domain. However this may be expected as healthy subjects who participated in regular exercise (defined as ≥ three exercise sessions per week), were excluded from the study. The main differences between COPD

subjects and healthy controls within the household domain can be attributed to control subjects preparing their own meals, using the stairs more often per day and 50% carrying out heavy housework. It could be that the questionnaire responses were related to gender roles rather than physical capabilities. For instance, several men reported that their wives had always done all of the cooking and cleaning. They would therefore score 0 for answering ‘never’ on these questions; despite being physically capable of these activities. Both groups used a car as their preferred means of transport to collect shopping, rather than walking, cycling or using public transport.

Patients with COPD generally discussed more sedentary leisure time activities compared to control subjects. However walking and gardening were the top two leisure activities enjoyed by both patients with COPD and healthy controls. However patients generally scored lower in these activities compared to controls because they were not able to walk for a long period or could only manage to pot plants rather than dig/ mow the lawn, for example. Therefore hours per week and intensity codes were much lower.

PA did not change after the 8-week RT programme described in this thesis. This was the case for both objective (ActiTrac®) and subjective (DASI) measures of PA were the effect sizes were 1.1 and 0.4 respectively. The reasons for this remain unclear. One possibility is that increases in strength are not routinely translated into changes in PA when RT is performed in isolation. The results may reflect the nature of the intervention which did not include any endurance training, education or PA advice. As quadriceps strength, thigh mass and whole-body exercise performance did significantly

improve after RT; it appears that these improvements are not translated into daily PA when the educational component of PR is missing. Whilst there continues to be limited research about the impact of education on PA, expert opinion suggest that there are important benefits of patient education to enhance behaviour change (Ries, Bauldoff, Carlin, Casaburi, Emery, Mahler, Make, Rochester, Zuwallack, & Herrerias 2007). Future work should explore how important changes in muscle strength and mass, associated with RT, can be translated into other measures (including PA) with the use of education or advice.

Another plausible explanation is that changes in PA take longer to become apparent, compared to the other outcome measures. As improved PA requires a long-term behaviour change, this may be facilitated by a longer treatment exposure (Ries et al. 2007). Therefore the PA outcomes may have shown significant changes if the programme were to continue beyond 8-weeks and measured at a later follow-up assessment (e.g. 6 and 12-months).

Finally, it could have been that the measures of PA were too crude to detect changes in PA. Whilst the monitors were sensitive enough to distinguish between walking speeds in the pilot study, they unfortunately lack the sophistication of other devices in terms of being able to detect time in different positions, energy expenditure (i.e. task difficulty) and does not report step counts. Whilst the monitors did detect movement in two planes, one can not be certain that this was walking or another purposeful activity. It may be that artefacts accounted for some of the movement detect, e.g. travelling by car.

Furthermore, the ActiTrac® reports PA in reference units (acceleration per minute) which may not be as meaningful to clinicians as EE (calories) or METS. These are more commonly used terms which relate better to PA intensity. This reduces the external validity of the device as it is difficult to routinely translate the findings to clinical practice and to compare PA outcomes from other studies using different devices. Furthermore, these arbitrary units are not useful for patients to use when trying to understand their progress following an intervention. In addition they could not be used by patients as a motivating factor or compliance aid for exercise training, as they give the wearer no feedback. These limitations are clearly a consideration when selecting a device for use in patients with COPD.

The ActiTrac® devices however, are more reasonably priced than other current devices on the market and may provide an affordable alternative when wishing to describe PA in the COPD population. If the area of interest is the outcome of rehabilitation or other interventions, more sophisticated devices would be preferred.

The relationship between estimated VO_2 max from the DASI and actual VO_2 recorded at peak exercise (incremental cycle ergometry) was found to be moderate (=0.59, $p<0.01$). However this relationship is not as strong as the relationship between the DASI and peak oxygen uptake in a cardiac population [correlation coefficient r= 0.80 (Hlatky et al. 1989)]. Further work is required to examine the agreement between peak VO_2 derived from the DASI and actual VO_2 from CPET in the COPD population and to compare the

agreement eith commonly employed field exercise tests (e.g. the ISWT). It may be that if the agreement is satisfactory (using Bland-Altman analysis) then the DASI could be used as a surrogate for a CPET or field walking test when the performance of these tests are impossible or impractical (e.g. in small community venues).

In conclusion, the data presented in this chapter has shown that the ActiTrac® activity monitors are reliable in the same wearer, reproducibly on consecutive occasions and can distinguish between slow, moderate and fast speeds of walking. These are important properties to consider when using accelerometers to describe populations or as an outcome measure.

The results in this chapter confirm that levels of PA are significantly lower in patients with COPD compared to healthy age-matched controls. Whilst quadriceps strength, thigh lean mass and whole-body exercise performance improved after the 8-week RT programme, PA did not change. This was the case for both objective and subjective measures of PA. This suggests that changes in strength are not routinely translated into PA improvements; there are a number of possible explanations for this finding.

Chapter 8

Discussion

The aim of this thesis was to explore the role of protein ingestion as an adjunct to RT and the effects on skeletal muscle function in patients with COPD and addresses gaps in the existing field of knowledge. Although RT is a key component of PR, the effects of this therapeutic combination (RT and protein supplementation) have never before been studied in this population.

The study hypothesis was that: RT, in combination with protein (at the time of training), will have greater effects on functional outcomes than RT alone. The main outcomes of the trial are reported in chapter 4. In addition, sub-studies were described which examine a number of other questions relating to the isokinetic RT measurements and outcomes of RT in more detail.

8.1 Main findings

The main outcomes of the RCT are reported in **chapter 4** and enable us to reject the study hypothesis. Protein did not augment the effects of RT as both COPD groups made significant improvements in all outcomes and there were no significant differences between the groups. These are novel findings as the effects of this therapeutic combination have never before been studied. Interestingly, despite patients with COPD exercising at lower absolute training intensities compared to healthy controls (**chapter 5**); they still made comparable (if not greater) improvements in all outcomes.

The increases in muscle strength and thigh lean mass, evident in all groups (**chapter 4**); support the idea that the RT programme was able to cause a net protein increase within the quadriceps muscle. It is unclear whether the RT programme increased protein synthesis, reduced degradation or a combination of the two. However the addition of protein did not enhance these effects and this was the case for both wasted and non-wasted sub-groups. The reasons for the apparent failure of the intervention are uncertain. It may have been that the response from RT swamps any additional effect of the protein or that the 'dose' of protein was not large enough. The response to protein may be dose-dependant and vary between individuals.

Despite being underpowered to detect significant changes in the wasted group, there was a suggestion that the wasted group responded less well to RT, compared to the non-wasted group (**chapter 4**). If these patients were in a negative protein balance prior to training (wasted), they may have required additional protein (in the diet or further supplementation) to ensure muscle protein synthesis. A poor treatment response in these patients may be attributed to an inadequate assessment of their energy requirements when engaged in the RT programme (Baarends et al. 1997a) as habitual diet was not recorded. It may have been that some of the 'wasted' patients fell into this 'non-responder' category and therefore reduced the effect of protein supplementation in the whole group.

Improvements in muscle mass and strength from RT were found to transfer to whole-body exercise performance, in terms work rate and some ventilation

variables (e.g. VO_2 max). The impressive changes of around 10 watts after RT (**chapter 4**), within each group, would typically be expected after endurance training (Lacasse et al. 2006) and suggests that the RT programme activated central systems. This is supported by findings in **chapter 6**, where it was apparent that patients with COPD were working at higher percentages of their maximal VO_2 (60%) and VE [72% (compared to a baseline CPET)] during RT, compared to healthy controls. This was despite control subjects training at significantly higher intensities. Furthermore, the HR for patients with COPD after RT was within the target HR training zone for cardio-respiratory fitness (66% of maximum).

Chapter 5 reports the data pertaining to the RT programme. The results showed that control subjects were working at higher absolute intensities for both work and torque at all time points, compared to patients with COPD. However the relative improvement in training progression (as a percentage from baseline) was greater in the COPD group. Although there appears to be a plateau at 4-weeks for training progression in control subjects, there were no significant differences between the groups for the training progression gradients. What was apparent was that control subjects became more FR during the 8-week programme, whilst COPD subjects did not. The reasons for this are unknown. However we may speculate that control subjects (who showed a plateau in training performance after 4-weeks) merely became more efficient at doing the same RT protocol towards the end of the programme. For patients with COPD, FR to this type of exercise may take longer to develop due to skeletal muscle dysfunction. Patients with COPD have a lower

oxidative capacity within the muscle and may therefore have been lacking the capacity (Allaire et al. 2004) to replenish oxygen within the muscles, during the RT programme. One may wonder weather healthy controls were able to do this, as their muscles have the usual oxidative preferences seen in normal elderly muscle (Lanza, Russ, & Kent-Braun 2004).

Changes in strength (around 20%) were found to be disconnected from changes in thigh muscle mass [(around 5%) **chapters 4 and** 5] and support previous findings that other factors, besides increased mass, are involved in producing muscle force (Jones et al. 2004). Although not directly measured, it is likely that neural adaptations accounted for a large proportion of the changes in strength. Neural adaptations occur within the first few weeks of training. One might have expected that the muscle mass changes would not be apparent until the 8-week measure, as muscle hypertrophy (change in fibre/ muscle group size) is known to occur later as a result of long-term training (Sale 1988). However, in the current study, there was a significant increase in muscle mass by week 4; at which point the majority of the improvement had occurred (**chapter 5**). Therefore changes in thigh mass would be unlikely to be any greater, even if the RT were to continue beyond 8-weeks. Interestingly changes in muscle mass showed no correlation with RT intensity (**chapter 5**).

Data presented in **chapter 5** also showed that the majority of improvements in strength also occurred within the first four weeks, for both groups. This is in line with the training intensity information, as most of the progression in work

and torque occurred in the first four weeks (**chapter 5**). There were some weak to moderate associations between training intensity (work/ torque) and the measures of isometric and isokinetic strength (60°/sec) after 8-weeks of training in both groups. These were positive, suggesting that increased training intensity leads to improved gains in muscle strength which are 'dose-dependant.

Chapter 7 evaluated the measurement properties of the ActiTrac® activity monitors. The data showed that these accelerometers were reliable in the same wearer on consecutive occasions. They are also sensitive to detect varying walking speeds. In this chapter it was also evident that COPD patients had lower levels of baseline PA compared to our age-matched control group (based on questionnaire data). However PA levels in patients with COPD did not change after the 8-week RT programme. This was the case for both objective (ActiTrac®) and subjective (DASI) measures and may indicate that changes in PA take longer to occur after RT, the measures were too crude to detect the change or simply that improvements in strength are not automatically translated into PA increases.

8.2 Implications for clinical practice

The routine recommendation of protein supplementation as an adjunct to RT in patients with COPD, can not be advocated based on the findings of this thesis (**chapter** 4).

The RT protocol described in this thesis would not constitute conventional RT typically employed in clinical practice. Isokinetic testing is rarely used in the evaluation of strength for patients with COPD and has not been used as a RT device in this population. However, the isokinetic protocol presented a unique opportunity to precisely explore the training intensity progression, fatigue profile (**chapter 5**) and cardio-respiratory load (**chapter 6**) imposed by the training; comparing patients with COPD and healthy controls. This enabled us to gather a detailed picture of RT in patients with COPD and to explore the relationship between RT intensity and outcome measures, such as strength which has previously been poorly described in the COPD population. The direct comparison of the training profiles in each group was also distinctive, as healthy populations are usually considered separately.

The changes in strength, thigh mass and whole-body exercise performance (**chapter 4**) after RT were of small to moderate effect size but are likely to be clinically meaningful for patients. Unfortunately there is no established MCID for changes in thigh mass, quadriceps strength or cycle ergometry ventilation outcomes in this population. This makes it difficult to interpret the findings, although the results are comparable to previous studies in healthy subjects and those with COPD. As the isokinetic RT programme described was able to influence both strength and endurance outcome measures (**chapter 4**) it is likely that the protocol sits fairly centrally on the continuum between resistance and endurance training. The training was able to sufficiently activate the cardio-pulmonary system (**chapter 6**) whilst symptom scores remained at acceptable levels. Therefore this RT protocol offers an attractive

alternative training option for breathless patients who perhaps can not sustain continuous aerobic training.

Changes in muscle strength were associated with training intensity, suggesting that strength improves in a 'dose-dependant' manner. Thigh lean mass was not correlated with training intensity and is perhaps not the most sensitive measure to use in this case. As most of the improvements in strength and thigh muscle mass occurred within the first 4-weeks (**chapter 5**); it may be that 4-weeks of RT is sufficient. Sewell and co-authors have previously reported that a four and seven-week PR programme were equivalent at the comparable time points of seven weeks and 6-months for SWT performance and HRQoL (Sewell et al. 2006). With ever constrained resources in the NHS, it may be important to demonstrate that we can produce significant improvements in RT outcomes within a short period of time. This would allow the distribution of limited resources to more patients, without compromising on quality.

Changes in isokinetic strength exceeded isometric strength changes in all groups (**chapter 4**). This is perhaps unsurprising, given that the training was also isokinetic in nature. However this may also suggest that isokinetic strength is more sensitive to change after RT and highlights the importance of measuring dynamic as well as static measures of strength. If only isometric strength is reported after training, important training adaptations may be overlooked. Also the association between peak torque progression in training

was greater with isokinetic rather than isometric strength and probably reflects the specific adaptation to the training which was also isokinetic (**chapter 5**). Furthermore, it was also noticed that changes occurred at the isokinetic testing velocity of 60°/sec even though training took place at 180°/sec. This transfer effect is in keeping with previous findings. This is encouraging as the slow velocity of 60°/sec would be difficult for patients to sustain during a training session. The 180°/sec training speed was known to target type II fibres (Jones et al. 2004) and the speed allowed for the acceptable completion of 5 sets of 30 maximal knee extensions in our frail COPD population, whilst still improving maximal strength at slower velocities.

Data presented in **chapter 5** highlighted that isokinetic work appears to be a more sensitive measure to change after RT and more susceptible to fatigue, compared to peak torque. This highlights the importance of measuring work which is cumulative rather than merely reporting peak torque (maximal force), as significant improvements may be missed. Furthermore, the test re-test reliability is equally very good for both isokinetic torque and work measures (see **appendix 11**).

In **chapter 4,** the recruitment of wasted subjects proved challenging, with only 12 subjects recruited who had FFMi evidence of muscle wastage. Therefore arbitrary FFMi cut-off values (less than 16 kg/m^2 in men or less than $15kg/m^2$ in women) were unhelpful in defining muscle wastage for this population. For this reason it may be more appropriate in clinical practice to observe muscle mass as a continuous variable and to look for natural cut-offs within the

spread of data. However it should be remembered that the FFMi cut-offs were based on BIA, rather than DEXA analysis and these methods are not interchangeable.

Although measuring FFM creates a challenge, I believe that the loss of lean or FFM is important to measure in the context of any rehabilitation programme for patients with COPD, where exercise may result in a negative energy balance. We know from work by Steiner and co-workers that an improvement in walking performance was related to the amount of carbohydrate ingested during a PR programme (Steiner et al. 2003) and that a lack of carbohydrate may have posed a limit to the amount of training patients could perform. The same may be true of protein during RT or conventional PR. The reasons for measuring FFM are two-fold: to ensure that adequate nutritional support can be given to overcome the metabolic demand of exercise and, secondly, to confirm that exercise is not exacerbating further lean mass loss. Indeed, the stimulus of exercise may be shown to improve weight gain by stimulating appetite. In the current study, habitual diet was not measured. This is perhaps a limitation and something to consider in outpatient rehabilitation programmes, particularly if there is a dietician available. In a busy outpatient environment, FFM could be measured using some of more portable measures, such as BIA, if DEXA is inaccessible.

The ActiTrac® activity monitor appears to be reliable in the same wearer, on consecutive occasions and able to detect walking speeds, based on findings in **chapter 7**. Importantly these accelerometers were sensitive enough to

detect slow speeds of walking, typically utilised by disabled patients with COPD. As the monitors are relatively inexpensive and simple to use, compared to others available on the market, they may provide an affordable alternative when wishing to describe PA in the COPD population. However the ActiTrac® lacks the sophistication of other devices and reports PA in arbitrary reference units which may not be meaningful to clinicians or patients requiring feedback. Furthermore, the individual characteristics of the activity monitors mean that they are not interchangeable and therefore the same monitor should be worn by the same individual on repeat testing.

The finding that improvements in strength do not routinely translate into PA benefits (**chapter 7**) is perhaps unsurprising, as the effects of RT on PA are inconclusive in this population. The results may reflect the nature of the intervention which did not include any endurance training, education or PA advice. As quadriceps strength, thigh mass and whole-body exercise performance did significantly improve after RT; it may be that these improvements are not routinely translated into daily PA when the educational section of PR is missing. This is important for PR practice as the educational component is likely to have a large impact upon lifestyle choices. This has not fully been explored and it is difficult to assess the impact of education alone as it is generally combined with exercise during PR programmes. Furthermore, as improved PA requires a long-term behaviour change, this may be facilitated by a longer treatment exposure or only become apparent after other outcome measures (Ries et al. 2007). Therefore the PA outcomes

may have shown significant changes if the programme were to continue beyond 8-weeks and if PA were measured at a later follow-up assessment.

The VO_2 max estimated from the DASI questionnaire, used in **chapter 7,** has a moderate correlation with the actual VO_2 measured by a CPET (r=0.59). This simple questionnaire may therefore offer an alternative when a SWT or CPET are impractical.

8.3 Suggestions for future work

In this study, protein did not augment the effects of RT, however the role of protein in the COPD population is worthy of future study. There was some suggestion in **chapter 4** that wasted patients responded less well to RT; however the effects of protein were equally as ineffective in wasted and non-wasted sub-groups. However there was insufficient study power to draw meaningful conclusions in the wasted group. Future work should explore the role of protein supplementation, particularly in wasted patients, during RT or conventional rehabilitation programmes. The titration of the correct dose of protein and the timing of protein in relation to training (e.g. during training) may be important variables to consider. As stated in section 8.2 the routine measurement of lean/ FFM before, during and after PR warrants consideration, as a negative energy balance during training may further exacerbate FFM loss and could limit the amount of training an individual can do. An understanding of the causes of energy imbalance and its relationship to the frequency, intensity and duration of exercise training would be of

interest to clinicians and could help to identify those in need of nutritional support.

The FFMi cut-off categories chosen in this study were unhelpful when defining muscle wastage in this population. Anecdotally it seemed that some individuals had a low BMI yet they failed to meet the FFMi wasting criteria. Furthermore, some individuals appeared to have wasted thigh muscles but as the FFMi is a total body measure, the wastage may not become apparent when other body compartments have preservation of FFM. As muscle wastage is an important problem for patients with COPD, other ways of defining muscle wastage are required. A composite measure or index of skeletal muscle dysfunction may be preferable which takes into consideration several factors, such as BMI, FFM, muscle strength and systemic inflammation. This type of index, in a similar way to the BODE, could then risk-stratify patients and help to identify those in need of different types of support (e.g. nutrition, RT). Alternatively, as the quadriceps muscles are predominately affected in patients with COPD, future research could develop FFM criteria based on thigh or quadriceps mass. This would involve generating normal values from measures taken in healthy individuals in the first instance. Future work could also evaluate the intra- and inter-observer variability in measuring the thigh ROI on DEXA analysis.

The data presented in this thesis confirms the effectiveness of RT in patients with COPD. However, most of the outcome measures described in this thesis, do not have established MCID values. This is a problem as one can judge

whether the results are clinically meaningful at an individual and group level, using these values. In future, it might be beneficial to derive MCID values for important outcomes after RT in patients with COPD, such as strength and quadriceps muscle mass, as has been the case for the outcomes of endurance training (e.g. ISWT). Furthermore it would be appropriate to explore the relatively sensitivity of outcome measures following RT, in the short and long-term.

The data regarding muscle fatigue is sparse in the COPD population, yet fatigue and FR are greatly important for exercise and daily task performance. In future, one may wish to explore which types of training and assessment protocols are the best at evoking fatigue in patients with COPD. Furthermore, it may be important to track how fatigue impacts upon exercise performance and whether FR occurs over time with different modes of training.

The relationship between RT intensity and outcome measures, such as strength has previously been poorly described in the COPD population. Ideally, the optimum 'dose' of training should depend on the individuals' needs and the ongoing measurement of outcomes during training (Ries et al. 2007). Although the serial measurement of outcomes may be impractical in the context of a PR programme, it may of benefit in the long-term. In **chapter 5** it was found that the majority of improvements in muscle strength and mass occurred within the first 4-weeks, beyond this additional improvements were minimal. Therefore the repeated measurement of outcomes during an exercise programme would be of merit. This would enable clinicians to train

individuals until they had made a pre-defined improvement in an outcome measure (e.g. MCID, % improvement, until there was 0 change from week to week) rather than fixing the programme length. This would enable limited resources to be shared between more individuals, without the quality of the programme being affected. In addition, it may be worthwhile training patients with their specific deficits in mind. For instance, if muscle weakness is a key problem then the PR programme should centre heavily upon RT. This is important as patients with muscle weakness may be done a disservice by generic PR programmes which concentrate on endurance training.

In future it would be interesting to see where the novel RT regime describes, sits on the spectrum between typical endurance and RT. It may be that we can tailor RT to suit individual needs based upon ventilatory parameters and comfort regarding respiratory symptoms. In addition, ventilatory and gas exchange measurements were only taken during a single RT session in this study (**chapter 6**); it would also be interesting to observe if the ventilatory load of training changes during the course of a RT programme. Finally, measures of lactate would have been of interest to compliment the results in **chapter 6** and measures of ventilation during the recovery phase after training warrant further exploration.

8.4 Concluding remarks

Skeletal muscle dysfunction is a key cause of exercise intolerance in patients with COPD, manifested by reduced muscle mass and strength, particularly affecting the quadriceps muscles. This problem also imposes a burden to the

health system as quadriceps dysfunction is an independent predictor of hospitalisation and mortality. Importantly, the quadriceps may provide a target for therapy in an otherwise irreversible lung disease and changes in strength after RT are well documented. Protein supplementation has been successfully used as an adjunct to RT in healthy populations. This thesis describes the first study to explore the role of this therapeutic combination in patients with COPD.

The overriding message from this thesis is that protein supplementation can not be routinely recommended as an adjunct to RT for patients with COPD. However it may have a role for those with evidence of muscle wastage and this warrants further research, as the current study was underpowered to detect significant improvements in this group. The dose of protein and the timing in relation to training may be important variables to manipulate. In any case, all groups made significant improvements in quadriceps strength and thigh mass after RT but protein did not augment the outcome. Subjects with COPD made comparable improvements to healthy age-matched controls, despite training at much lower intensities and experiencing more fatigue. Moreover, the RT programme was able to sufficiently activate the cardio-pulmonary system and led to significant improvements in whole-body exercise performance. PA did not change after the 8-week RT programme; suggesting that changes after RT are not routinely translated to increased habitual PA, particularly when the educational component of rehabilitation is absent.

The isokinetic RT programme used in this thesis provided a unique opportunity to precisely explore the training intensity progression, fatigue profile and cardio-respiratory load imposed by the training; comparing patients with COPD and healthy controls. The findings from this work provide some important considerations for clinical practice (section 8.2) and require further investigation within a conventional rehabilitation setting.

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Appendix 1

ELSEVIER

Physiotherapy

Physiotherapy 95 (2009) 1–7

Narrative review

How sustainable is strength training in chronic obstructive pulmonary disease?

Linzy Houchen [a,*], Michael C. Steiner [a], Sally J. Singh [a,b]

[a] *Pulmonary Rehabilitation Research Group, Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester LE3 9QP, UK*
[b] *Faculty of Health and Life Sciences, Coventry University, Coventry CV1 5FB, UK*

Appendix 2

Physiotherapy 97 (2011) 264–266

Short communication

Preservation of lower limb strength after a short course of pulmonary rehabilitation with no maintenance: a 6-month follow-up study

Linzy Houchen [a,b,*], Sarah Deacon [a], Carolyn Sandland [a], Rachael Collier [a], Michael Steiner [a], Michael Morgan [a], Sally Singh [a,b]

[a] *University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK*
[b] *Faculty of Health and Life Sciences, Coventry University, Coventry, UK*

Appendix 3

PATIENT INFORMATION SHEET

Molecular Approaches to Reversing Skeletal Muscle Wasting in COPD. The Role of Resistance Training and Protein Supplementation.

Principal Investigator: **Dr Michael Steiner**

Co-Researchers: **Prof Sally Singh**
Dr. Michael Morgan
Dr Manoj Menon
Ms Linzy Houchen

You may contact: **Dr. Michael Steiner**
0116 256 3450

This study is sponsored by the **Medical Research Council**.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this study?

A large number of people in the UK have long term breathing problems due to lung diseases such as Chronic Obstructive Pulmonary Disease (COPD). Patients with these conditions experience breathlessness when they try to exercise or perform physical tasks. In many patients this is made worse by weakness and wasting of the leg muscles. However, little is known about the underlying reasons for muscle wasting in patients who suffer with COPD. It is known that certain genes are involved in regulating the size and strength of the leg muscles in healthy humans. Recent research has shown that these genes are important in the increase in muscle bulk seen after exercise training in healthy people, particularly when exercise is combined with additional dietary protein intake. However, we don't know if these genes are important in muscle wasting in patients who have COPD. We know that exercise training is effective in improving symptoms for patients with COPD. However the mechanisms by which these improvements are brought about are largely unknown.

The aim of this research is to study the effects of a programme of exercise training and dietary supplementation on functioning of these genes in

patients who suffer with COPD. We will compare these effects in similar aged healthy volunteers.

This knowledge will help us understand why muscle wasting happens in patients with lung diseases such as COPD. This is important because if we can understand how our genes regulate these changes in muscle bulk we may be able to develop new treatments to address this problem in patients with chronic diseases such as COPD.

Why have I been chosen?

Members of the pulmonary rehabilitation research team are conducting this study in collaboration with Prof Paul Greenhaff at the University of Nottingham. Patients with COPD who are going to attend the outpatient pulmonary rehabilitation programme or who are attending out patients at Glenfield Hospital are being invited to participate. We are also inviting similar aged healthy individuals who do not have lung disease to participate.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part?

The purpose of this research study is to determine the effects of a programme of leg exercise training combined with dietary supplements. If you agree to participate, you will therefore be asked to undertake an eight-week programme of leg (quadriceps muscle) training.

Because we don't know whether taking additional dietary supplements is helpful, patients will be put into two groups and then compared. The groups are selected by a computer, which has no information about the individual – i.e. by chance. One group will receive a dietary supplement drink and the other group will receive an inactive dummy drink (called a placebo). Neither you nor your doctor will know in which treatment group you are (although, if your doctor needs to find out he/she can do so).

In order to find out what the effects of these treatments is, you will be asked to attend the hospital for additional assessments before the start of the exercise programme, in the middle of the programme and at the end. Some of these assessments will require a specific visit to hospital. Others will be performed on a day you are attending anyway as part of the exercise programme.

Your involvement in the study will last 10 to 12 weeks. The study overall will be running for around three and a half years.

Exercise Programme

You will be asked to attend Glenfield Hospital three times a week to exercise both legs on a piece of equipment called a "Cybex". This will involve extending your leg as hard as you can on the Cybex. We will ask you to do

this 15 to 30 times (also called “repetitions”). There will be up to five bouts of these repetitions. You will be able to rest between these bouts.

Dietary Supplement

Depending on which group you are put in you will be asked to drink a dietary supplement or a placebo immediately after each bout of exercise during the exercise programme.

Assessment Visits

Visit 1

During this visit a doctor will discuss the study with you, take a medical history and examine you. You will also complete a questionnaire which asks about your daily physical activity. You will then be asked to perform breathing tests, which involves taking deep breaths, holding your breath and blowing down a tube. We will also measure your height and weight. We will also ask you to have a practice run at exercise on a bike and on the Cybex.

Visit 2

We will ask you to perform an exercise test on a special bicycle to establish your exercise ability. During the exercise we will record your heart and oxygen levels and you will breathe in and out of a mouthpiece. The bike will get gradually harder to pedal until you ask to stop. You will then be asked to perform a test to measure strength in your thigh muscle. This will involve sitting on a chair and extending your leg (which is attached to a lever) as hard as you can for a few seconds against a resistance.

You will also have a DEXA Scan. This measures the amount of fat, muscle and bone in your body. The scan is painless and requires you to lie flat for a few seconds.

The exercise programme will start one to two weeks after visit 2. During this time you may be asked to wear an activity monitor at home for 7 days. This will count the times that you are active throughout the day and can be hidden under your clothing.

Visit 3

On the first day you attend for the exercise programme we will take a small sample of muscle from your thigh. This is called a muscle biopsy. Local anaesthesia is used to numb the area and a special needle is inserted through a small incision in the skin into the thigh muscle. We will also obtain a sample of blood from a forearm vein. Your first exercise session of the programme will be performed after these tests.

Visit 4

The day after your first exercise session we will take another muscle biopsy from your thigh. We will also take another blood test.

Visit 5

Before one of your exercise sessions in the 4th or 5th week of the programme we will take another muscle biopsy, blood test, and another DEXA Scan.

Visit 6

We will ask you to attend Glenfield Hospital after the exercise programme has been completed. We will take another muscle biopsy and another blood test. We will then ask you to repeat the test of muscle strength and the cycle test. You will have a final DEXA Scan and be asked to complete the physical activity questionnaire again. If you wore an activity monitor before the training programme we will ask you to wear one again for another 7 days at home.

We would like to see whether the benefits of the strength training programme are maintained. We will therefore invite you to visit us 6 months after you have finished the training programme to re-test your muscle strength. This visit will be optional.

Travel Arrangements

The study involves a number of visits to hospital. Travel by taxi for all these visits will be provided for you if you need or wish it.

What will happen to samples I donate as part of this study?

Muscle and blood samples you provide during the study will be stored and analysed at Nottingham University under the supervision of Prof Paul Greenhaff. Some of the analysis will take place after the study has been completed and samples may be stored for up to five years. Any remaining tissue will be destroyed at the end of the study and will not be used for any other purpose or future research. The samples you donate will not be tested for genetic diseases or other conditions.

What do I have to do?

Other than detailed above, you will not have to make any changes to your medication or lifestyle.

What are the possible benefits of taking part?

We would expect you to benefit from improvements in muscle strength as a result of the exercise programme although this may not occur in all participants. If the dietary supplement proves beneficial you may benefit also from this if you are placed in the active treatment group.

We hope the information we get from this study will be helpful in understanding the problem of muscle wasting in patients with COPD and developing new treatments for this problem.

What are the possible disadvantages and risks of taking part?

You may find the muscle biopsy uncomfortable. Your thigh may ache for a day or two after the biopsy. If the biopsy site is uncomfortable we can

provide painkillers for you. There is a very small risk that the site of biopsy could bleed or become infected.

The DEXA scans involve a very small exposure to x-rays. This is equivalent to a fraction of that involved in having a standard chest X-ray. A greater exposure would occur naturally from the environment if you were to take a two week holiday in Cornwall.

There is a very small risk of injury from performing the exercise.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

Will my taking part in this study be kept confidential?

Yes. Your personal details and all information collected about you during this study will be held in strictest confidence. People organising the trial may see your medical records but in no circumstance will personal details be made available to the public. We will inform your GP that you are taking part in the study. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised. If the results of the study are published you will not be identified in the report.

Who has reviewed the study?

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If you have any questions please do not hesitate to contact:

Dr Manoj Menon Tel 0116 258 3652
Dr. Michael Steiner Tel 0116 256 3450

Thank you for reading this information leaflet.

Appendix 4

HEALTHY VOLUNTEER INFORMATION SHEET

Molecular Approaches to Reversing Skeletal Muscle Wasting in COPD. The Role of Resistance Training and Protein Supplementation.

Principal Investigator: **Dr Michael Steiner**

Co-Researchers: **Prof Sally Singh**
Dr. Michael Morgan
Dr Manoj Menon
Ms Linzy Houchen

You may contact: **Dr. Michael Steiner**
0116 256 3450

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A large number of people in the UK have long term breathing problems due to lung diseases such as Chronic Obstructive Pulmonary Disease (COPD). Patients with these conditions experience breathlessness when they try to exercise or perform physical tasks. In many patients this is made worse by weakness and wasting of the leg muscles. However, little is known about the underlying reasons for muscle wasting in patients who suffer with COPD. It is known that certain genes are involved in regulating the size and strength of the leg muscles in healthy humans. Recent research has shown that these genes are important in the increase in muscle bulk seen after exercise training in healthy people, particularly when exercise is combined with additional dietary protein intake. However, we don't know if these genes are important in muscle wasting in patients who have COPD. We know that exercise training is effective in improving symptoms for patients with COPD. However the mechanisms by which these improvements are brought about are largely unknown.

The aim of this research is to study the effects of a programme of exercise training and dietary supplementation on functioning of these genes in patients who suffer with COPD. You are being asked to take part because we need to compare these effects in healthy people of a similar age.

This knowledge will help us understand why muscle wasting happens in patients with lung diseases such as COPD. This is important because if we can understand how our genes regulate these changes in muscle bulk we may be able to develop new treatments to address this problem in patients with chronic diseases such as COPD.

Why have I been chosen?

Members of the pulmonary rehabilitation research team are conducting this study in collaboration with Prof Paul Greenhaff at the University of Nottingham. You have been invited to participate as a healthy subject who does not have lung disease. Patients with COPD who are attending out-patient departments at Glenfield Hospital are also being invited to participate.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part?

The purpose of this research study is to determine the effects of a programme of leg exercise training combined with dietary supplements. If you agree to participate, you will therefore be asked to undertake an eight-week programme of leg (quadriceps muscle) training. Healthy volunteers who agree to participate will not need to take the supplements.

In order to find out what the effect of the training programme is, you will be asked to attend the hospital for additional assessments before the start of the exercise programme, in the middle of the programme and at the end. Some of these assessments will require a specific visit to hospital. Others will be performed on a day you are attending anyway as part of the exercise programme.

Your involvement in the study will last 10 to 12 weeks. The study overall will be running for around three and a half years.

Exercise Programme

You will be asked to attend Glenfield Hospital three times a week to exercise both legs on a piece of equipment called a “Cybex”. This will involve extending your leg as hard as you can on the Cybex. We will ask you to do this 15 to 30 times (also called “repetitions”). There will be up to five bouts of these repetitions. You will be able to rest between these bouts.

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During this visit a doctor will discuss the study with you, take a medical history and examine you. You will also complete a questionnaire which asks about your daily physical activity. You will then be asked to perform breathing tests, which involves taking deep breaths, holding your breath and blowing down a tube. We will also measure your height and weight. We will also ask you to have a practice run at exercise on a bike and on the Cybex.

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We will ask you to perform an exercise test on a special bicycle to establish your exercise ability. During the exercise we will record your heart and oxygen levels and you will breathe in and out of a mouthpiece. The bike will get gradually harder to pedal until you ask to stop. You will then be asked to perform a test to measure strength in your thigh muscle. This will involve sitting on a chair and extending your leg (which is attached to a lever) as hard as you can for a few seconds against a resistance.

You will also have a DEXA Scan. This measures the amount of fat, muscle and bone in your body. The scan is painless and requires you to lie flat for a few seconds.

The exercise programme will start one to two weeks after visit 2. During this time you may be asked to wear an activity monitor at home for 7 days. This will count the times that you are active throughout the day and can be hidden under your clothing.

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We will ask you to attend Glenfield Hospital after the exercise programme has been completed. We will take another muscle biopsy and another blood test. We will then ask you to repeat the test of muscle strength and the cycle test. You will have a final DEXA Scan and be asked to complete the physical activity questionnaire again. If you wore an activity monitor before the training programme we will ask you to wear one again for another 7 days at home.

We would like to see whether the benefits of the strength training programme are maintained. We will therefore invite you to visit us 6 months after you have finished the training programme to re-test your muscle strength. This visit will be optional.

Travel Arrangements

The study involves a number of visits to hospital. Travel by taxi for all these visits will be provided for you if you need or wish it.

What will happen to samples I donate as part of this study?

Muscle and blood samples you provide during the study will be stored and analysed at Nottingham University under the supervision of Prof Paul Greenhaff. Some of the analysis will take place after the study has been completed and samples may be stored for up to five years. Any remaining tissue will be destroyed at the end of the study and will not be used for any other purpose or future research. The samples you donate will not be tested for genetic diseases or other conditions.

What do I have to do?

Other than detailed above, you will not have to make any changes to your medication or lifestyle.

What are the possible benefits of taking part?

We would expect you to benefit from improvements in muscle strength as a result of the exercise programme although this may not occur in all participants. We hope the information we get from this study will be helpful in understanding the problem of muscle wasting in patients with COPD and developing new treatments for this problem.

What are the possible disadvantages and risks of taking part?

You may find the muscle biopsy uncomfortable. Your thigh may ache for a day or two after the biopsy. If the biopsy site is uncomfortable we can provide painkillers for you. There is a very small risk that the site of biopsy could bleed or become infected.

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There is a very small risk of injury from performing the exercise.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

Will my taking part in this study be kept confidential?

Yes. Your personal details and all information collected about you during this study will be held in strictest confidence. People organising the trial may

see your medical records but in no circumstance will personal details be made available to the public. We will inform your GP that you are taking part in the study. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised. If the results of the study are published you will not be identified in the report.

Who has reviewed the study?

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If you have any questions please do not hesitate to contact:

Dr Manoj Menon	Tel 0116 258 3652
Dr. Michael Steiner	Tel. 0116 256 3450

Thank you for reading this information leaflet.

Appendix 5

Participant Identification Number for this trial:

CONSENT FORM

Molecular Approaches to Reversing Skeletal Muscle Wasting in COPD. The Role of Resistance Training and Protein Supplementation.

Principal Investigator: **Dr Michael Steiner**

Co-Researchers: **Prof Sally Singh**
Dr. Michael Morgan
Dr Manoj Menon
Ms Linzy Houchen

Please initial box

1. I confirm that I have read and understand the information sheet dated 04/06/2007 (version 4) for the above study and have had the opportunity to ask questions ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Cybex Training- Data Collection

Isokinetic Training: 5 sets of 30reps at 180°/sec

WB | Week No:

Day 1. Session No:

	Pre	Post
Borg		
RPE		
SpO_2		
HR		

Right

	Torque	Work
1		
2		
3		
4		
5		
Highest		

Left

	Torque	Work
1		
2		
3		
4		
5		
Highest		

Supplement/ Placebo Given?

Day 2. Session No:

	Pre	Post
Borg		
RPE		
SpO_2		
HR		

Right

	Torque	Work
1		
2		
3		
4		
5		
Highest		

Left

	Torque	Work
1		
2		
3		
4		
5		
Highest		

Supplement/ Placebo Given?

Day 3. Session No:

	Pre	Post
Borg		
RPE		
SpO_2		
HR		

Right

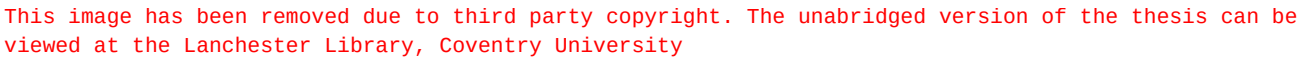
	Torque	Work
1		
2		
3		
4		
5		
Highest		

Left

	Torque	Work
1		
2		
3		
4		
5		
Highest		

Supplement/ Placebo Given?

Appendix 7a


This image has been removed due to third party copyright. The unabridged version of the thesis can be viewed at the Lanchester Library, Coventry University

Appendix 7b

Ingredients in the Placebo are: water, dextrin (starchfibre), aroma, acidifier (citric acid), xanthangum, titanium dioxide, colour (red beat powder), sweetener (aspartame, acesulfam-K)

Appendix 8

THE BORG BREATHLESSNESS SCORE

0	**NOTHING AT ALL**
0.5	**VERY, VERY SLIGHT**
1.0	**VERY SLIGHT**
2.0	**SLIGHT**
3.0	**MODERATE**
4.0	**SOMEWHAT SEVERE**
5.0	**SEVERE**
6.0	
7.0	**VERY SEVERE**
8.0	
9.0	**VERY, VERY SEVERE (ALMOST MAXIMAL)**
10	**MAXIMAL**

(N.B. There is no ‘right’ or ‘wrong’ way with this scoring. It is just how you feel at the time. It is helpful for us to know how difficult you find each exercise.)

Appendix 9

HOW HARD WAS IT?

7 VERY, VERY LIGHT
8
9 VERY LIGHT
10
11 FAIRLY LIGHT
12
13 SOMEWHAT HARD
14
15 HARD
16
17 VERY HARD
18
19 VERY, VERY HARD

Appendix 10

A comparison of 3 methods to measure isometric quadriceps strength

Introduction: The measurement of skeletal muscle strength is important in the assessment of RT programmes in patients with COPD. The test re-test reliability of repeated measures taken within the same session is important to establish to ensure that learning and fatigue effects are accounted for.

Aim: The purpose of this study was to evaluate the test-retest reliability of three measures of isometric quadriceps strength in patients with COPD and healthy controls.

Methods: The data from16 patients with COPD [mean (SD) age 68.6 (8.2) years, FEV_1 47.8 (23.0) % predicted,13 male] and 11 healthy subjects [mean (SD) age 66.4 (4.7) years, FEV_1 97.3 (25.7) % predicted, 6 male] was available for analysis. Isometric peak force was measured using the microFET2 handheld dynamometer (HHD), a seated strain gauge (SG: Kern) and the Cybex II Norm isokinetic dynamometer. The knee angle was fixed at 70° flexion for all testing methods. All were performed at least three times on two occasions within the same session, at least 30 minutes apart.

The HHD and SG measure strength in Kg. This was converted to Newtons (N) to allow comparison with the Cybex. The intra class correlation co-efficient (ICC) was calculated for all three measures.

Results: Table1 shows the mean values for isometric strength for all testing methods, on both tests, mean difference between the two tests and the ICC.

Conclusions: The ICC was high for all isometric strength measures and very high for the SG and the Cybex [according to previously reported values (Munro 2001)]. The HHD was slightly less reliable on repeat testing. There does not appear to be a significant learning effect and the results were comparable between patients and healthy controls.

	Method	**Mean(SD)**		**Mean difference between Tests 1 and 2 (95% CI)**	**ICC**
		Test 1	**Test 2**		
COPD	HH (N)	167.2(34.7)	169.2(29.0)	2.1 (-20.3-16.1)	.714
	SG (N)	267.8(54.3)	273.4(60.1)	5.6 (-33.2-22.0)	.909
	Cybex (Nm)	124.7(43.7)	132.4(47.5)	7.7 (-20.5-5.1)	.931
Healthy	HH (N)	160.1(29.0)	172.6(28.5)	13.0 (-27.2-2.2)	.854
	SG (N)	273.4(54.3)	288.5(97.4)	15.1 (-65.4-35.2)	.905
	Cybex (Nm)	131.9(41.4)	134.0(56.2)	2.1 (-22.0-17.8)	.914

Table 1.

Appendix 11

Report: test re-test reliability of isokinetic methods to measure quadriceps muscle function

Introduction: Isokinetic testing is a sophisticated method to assess muscle function and relates closely to functional movements; more so than isometric testing and has been extensively reported in musculoskeletal rehabilitation (Mathur, Makrides, & Hernandez 2004). However isokinetic testing is unfamiliar to most individuals and is rarely used in the assessment and training of individuals with COPD. Only 16 out of 139 articles relating to RT in patients with COPD used an isokinetic dynamometer to measure dynamic strength (Robles, Mathur, Janaudis-Fereira, Dolmage, Goldstein, & Brooks 2011). This systematic review found that most of these studies measured quadriceps strength at 60°/sec.

Reliability results from isokinetic testing in the healthy population can not be easily transferred to patients with COPD who have weaker muscles and are more prone to fatigue (American Thoracic Society/ European Respiratory Society 1999). Test re-test reliability of repeated measures taken within the same session is important to establish to ensure that learning and fatigue effects are accounted for. The test re-test reliability of isokinetic muscle testing has therefore been explored in patients with COPD. In 2004, Mathur and colleagues reported within-session and test re-test reliability over seven days for isokinetic strength testing in 20 patients with moderate to severe

COPD (Mathur, Makrides, & Hernandez 2004). Isokinetic testing of the quadriceps took place on the dominant leg for three trials at PAV's of 30 and 90 °/sec. The within-session test re-test reliability was high [intra-class correlation co-efficients (ICCs) ranging from 0.95 (90°/sec) to 0.99 (30°/sec)]. There were no significant differences between the three trials ($p>0.05$). There were also no significant differences between the peak torque recorded between two sessions, one week apart [ICC 0.85 (30°/sec) and 0.96 (90°/sec)]. However this study did not observe the reliability at the testing velocity of 60°/sec, chosen in this RCT. Furthermore, the authors did not report the test re-test reliability of work. Isokinetic work may have different test re-test properties compared to peak torque.

Aims: The aim of this chapter was to assess the test re-test reliability of the chosen isokinetic testing protocol (60°/sec) in patients with COPD; considering both peak torque and total work variables, analysed within one session. A secondary aim was to compare the reliability between patients with COPD and healthy, age-matched controls.

Methods: Testing of the dominant quadriceps took place on an isokinetic dynamometer (Cybex II Norm, CSMi, Stoughton, MA, USA) as described in chapter 3 (materials and methods). Subjects performed two sets of five knee extensions at 60 °/sec. Knee ROM was set between 10-80° flexion. The highest peak torque (Nm) and total work (J) were recorded. Repeat testing was performed on two subsequent occasions after a rest period of at least 30

minutes, on the same day. These measures took place on the familiarisation session, prior to baseline testing and the start of RT.

Statistical Analysis: A repeated measures analysis of variance (ANOVA) with post-hoc Bonferroni testing was used to identify any significant differences between the peak torque and total work done on the three tests. The *F* statistic, along with its degrees of freedom (df) are reported.

Agreement between tests 1, 2 and 3 (for torque and work) was calculated according to the method of Bland and Altman, with the magnitude of differences expressed as the mean difference (*d)* and the limits of agreement calculated from 2 standard deviations (SD) of the differences.

Finally ICCs were also calculated for torque and work. ICC values of 0.70 to 0.89 were accepted as high reliability, values of 0.90 and above represented very high reliability (Munro 2001).

Results: A sample of 57 subjects with COPD [39 male, mean (SD) age 68.6 (8.9) years, FEV_1 45.6 (15.6) percent predicted, BMI 27.0 (5.3)] and 17 healthy age-matched controls [9 male, mean (SD) age 67.0 (4.5) years, FEV_1 103.4 (15.9) percent predicted, BMI 27.7 (2.6)] completed three strength assessments on a familiarisation visit, prior to starting the RT programme.

Mean values and percentage differences between tests are shown in table 1 for both isokinetic torque and work, for both groups. For COPD patients, there

were significant differences between the three tests for isokinetic peak torque, *F* (df 2, 112) = 4.36. Post-hoc tests revealed that the significant differences were between tests 1 & 2 and tests 1 & 3 (both p<0.05), but not between tests 2 & 3 (p>0.05). For isokinetic work in COPD patients there were also significant differences between the tests, *F* (df 2, 100) = 7.57. Sphericity was violated for work; therefore a Greenhouse-Geisser correction was made. Again post-hoc tests revealed that the significant differences were between tests 1 & 2 and tests 1 & 3 (both p<0.01), but not between tests 2 & 3 (p>0.05).

Table 1. Mean values for isokinetic torque and work on 3 testing occasions for patients with COPD and healthy controls

	Test 1	**Test 2**	**Test 3**
COPD Subjects			
Mean (SD) isokinetic torque (Nm)	80.0 (31.9)	83.8 (34.0)*	83.6 (35.7)*
Mean percentage change between tests (95%CI)	----------	5.2 (1.6-8.8)	-0.6 (-4.4-3.2)
Mean (SD) isokinetic work (J)	286.4 (121.4)	308.8 (137.5)**	312.4 (147.2)*
Mean percentage change between tests (95%CI)	----------	8.2 (3.2-13.2)	2.1 (-5.4-9.6)
Healthy Subjects			
Mean (SD) isokinetic torque (Nm)	97.9 (30.0)	98.8 (30.8)	99.2 (33.5)
Mean percentage change between tests (95%CI)	----------	2.2	-0.6
Mean (SD) isokinetic work (J)	373.1 (130.2)	375.2 (124.9)	377.2 (139.4)
Mean percentage change between tests (95%CI)	----------	1.3	-0.5

****p<0.01, * p<0.05 significant difference from test 1.**

When performing the repeated measures ANOVA for isokinetic torque in healthy subjects, sphericity was violated. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. The results showed no significant differences between the 3 tests, F (df 1.47, 23.50) = 0.19 ($p > 0.05$). Similarly, there were no significant differences between the three tests for isokinetic work in healthy subjects; F (df 2, 32) = 0.08 ($p > 0.05$).

The mean of the individual differences (d) in isokinetic torque and work between tests (test 2 minus test 1 etc) and limits of agreement [± 2 SD of the differences (d)], are shown in figure 1 for subjects with COPD. Acceptable limits of agreement for this type of testing are unknown. Inspection of the Bland and Altman plots suggests that the differences are sporadic and do not become more variable at high or low torque/ work values.

The ICC values for isokinetic torque were 0.98 for patients with COPD and 0.97 for healthy controls. For isokinetic work, the ICC values were 0.97 for patients with COPD and 0.98 for control subjects.

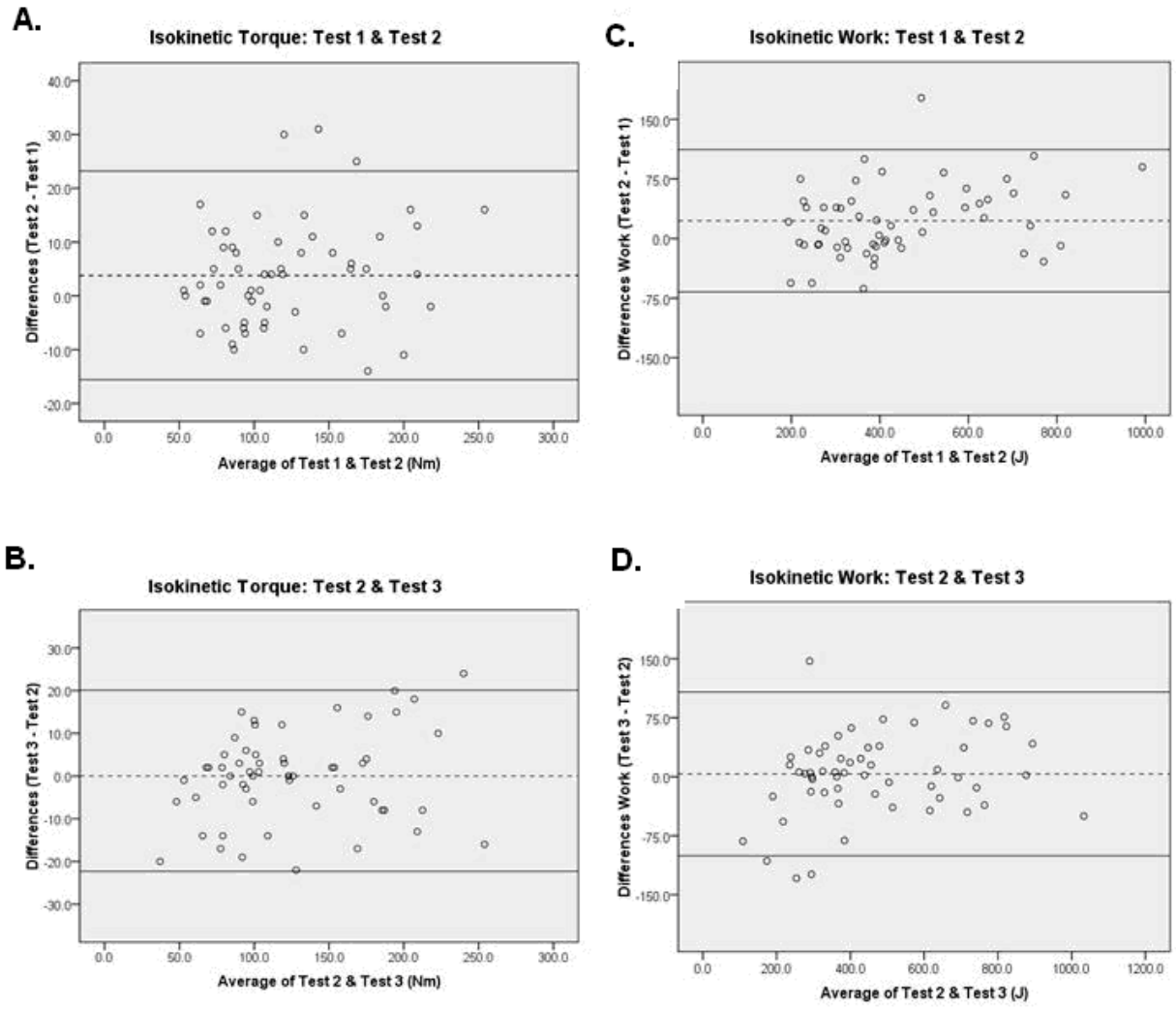


Figure 1 Bland and Altman plots of the difference between tests 1 & 2 and tests 2 & 3 for isokinetic torque (A and B) and work (C and D) for patients with COPD

Conclusion: For patients with COPD, the results show statistically significant differences between tests 1 and 2 but not between tests 2 and 3 for both isokinetic torque and work. However the percentage change between repeat tests was relatively small in comparison to changes in isokinetic strength evident after the 8-week RT programme (see chapter 4). Inspection of the Bland and Altman plots suggests that the differences between tests were sporadic and do not become more variable at high or low torques and work

rates. Acceptable limits of agreement for this type of testing are unknown. These results suggest that subjects with COPD should perform at least one familiarisation test prior to baseline testing when using this unfamiliar strength testing method. This would be considered best practice.

For healthy subjects, there were no significant differences between repeat tests for both peak torque and work. The cause of this apparent stability is unknown, particularly when the testing method would also be unfamiliar to most healthy individuals also. As with all types of strength testing, the results may be effort dependant. One may speculate that perhaps patients with COPD would be more tentative on the first testing occasion due to fears over breathlessness and perceived exertion of the task. This may account for the greater difference between tests one and two in patients with COPD, compared to healthy controls.

The ICC values were very high for both torque (0.98) and work (0.97) in patients with COPD. Therefore the test re-test reliability for torque and work are similar. The ICC value for torque presented here, is similar to that reported within a single session by Mathur and co-workers (Mathur, Makrides, & Hernandez 2004); 0.95 (90°/sec) and 0.99 (30°/sec). Furthermore, there were no significant differences between ICC values for patients with COPD and healthy age-matched controls in the current study.

Appendix 12

Equipment calibration procedures

Isokinetic dynamometer

The isokinetic dynamometer (Cybex II Norm: CSMi, Stoughton, USA) was calibrated every month in accordance with manufacturer's guidelines. This involved placing 100lbs of weight onto the knee/hip adapter arm which was set at a specific length. The weight was then dropped and the system shows the amount of torque that it should read when 100lbs is dropped. Following this weight drop, the system adjusts its internal conversion factors. 'Success' will be displayed if the calibration is ok. If there is an error, the calibration should be repeated before contacting CSMi for technical support.

DEXA Scanner

The DEXA scanner was calibrated daily with a Quality Assurance (QA) test; as suggested by the manufacturer. This involved placing a calibration block under the laser light of the DEXA scanner arm. The block consists of tissue-equivalent material with three bone-simulating chambers of known bone mineral content. The remainder of the test runs automatically; testing the detector status, bone mineral density of the block and system status. The software automatically returns to the QA screen once the test is completed. A green light indicates a pass and is a sign that the system is ready to measure patients. A red light indicates a fail. In this scenario the test should be repeated before calling the manufacturer for assistance.

Cycle ergometer

Gas calibration was performed everyday, in line with manufacturer recommendations. Prior to calibration the system had to be switched on for a minimum warm-up time of 20 minutes. The gas calibration involved opening the gas bottle and connecting the gas-suction tube to the calibration port on the front panel of the Zan 600. Gas mixture I (bottle gas) is compared to gas mixture II (ambient air). The actual values are displayed together with the expected values before the calibration is complete.

Volume calibration is performed before each individual test, in accordance with manufacturer guidelines. To do this, the flow sensor is connected to a 3l calibration syringe. The piston of the syringe is moved from end to end for six strokes and the results of the calibration are shown. If the calibration volume equals the syringe volume then the calibration is successful. If the deviations are too large, the test is repeated before contacting the manufacturer for support.

In addition, a biological quality control test was carried out monthly starting 1 year prior to the study start and during the study; using a young human male subject. After several practice tests, baseline tests were performed over a short period of time. All tests were then compared to these baseline values. The test involved a maximal incremental cycle ergometry test using a ramp protocol. The load was increased by 30W/min after a 1-minute warm-up (no load).

Respiratory Physiology Equipment

The SPIRO AIR® equipment was calibrated every morning for volume, FRC and transfer factor. A green light is displayed as a pass for all three tests. If a fail occurs, the calibration should be re-done before contacting the manufacturer for assistance. A healthy, young biological control used the equipment every 3-weeks as a further quality control measure.

The blood gas analyser uses a two point calibration to check expected and actual concentrations of O_2, carbon dioxide CO_2 and pH. This occurs automatically every two hours. A further quality control is completed every 2-weeks where 3 known levels (low – high) of O_2, CO_2 and pH are analysed by the system. These should be within 2 SD of what is expected.

Appendix 13

Resistance training progression for the left leg

This appendix shows the equivalent graphs and tables for the left leg that are displayed for the right leg in chapter 5.

They are: total work progression, peak torque progression, percentage progression in training variables, fatigue indexes for total work and peak torque and absolute total work and torque decline over the 8-week training period.

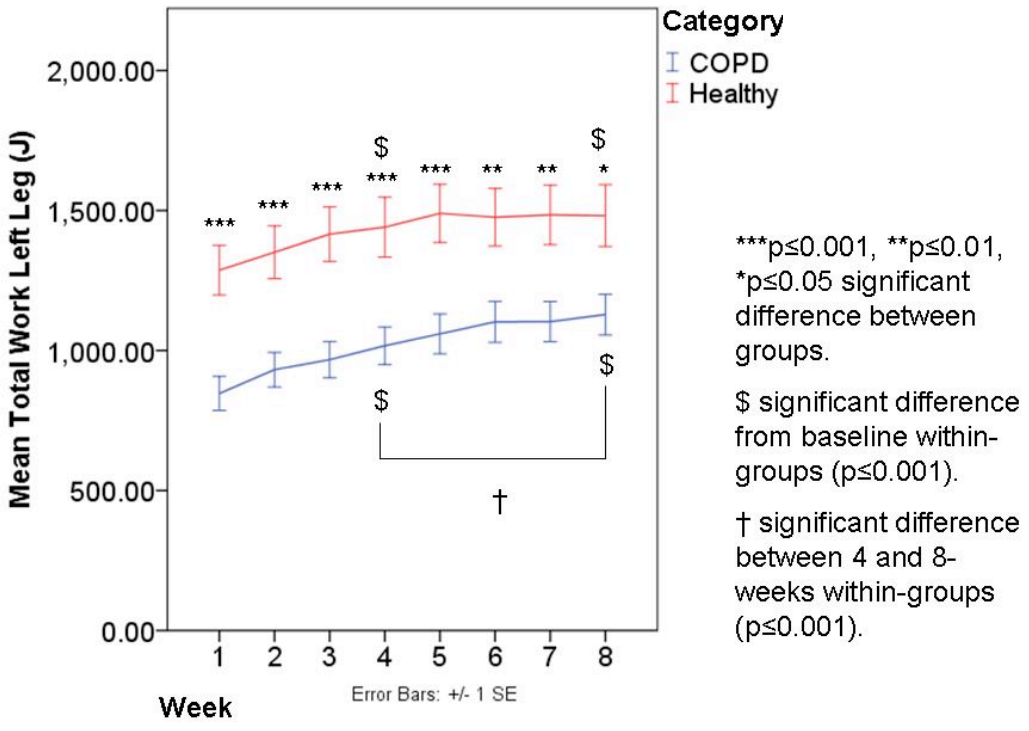


Figure 1. Training intensity progression of total work performed at weeks one to eight in patients with COPD and healthy controls

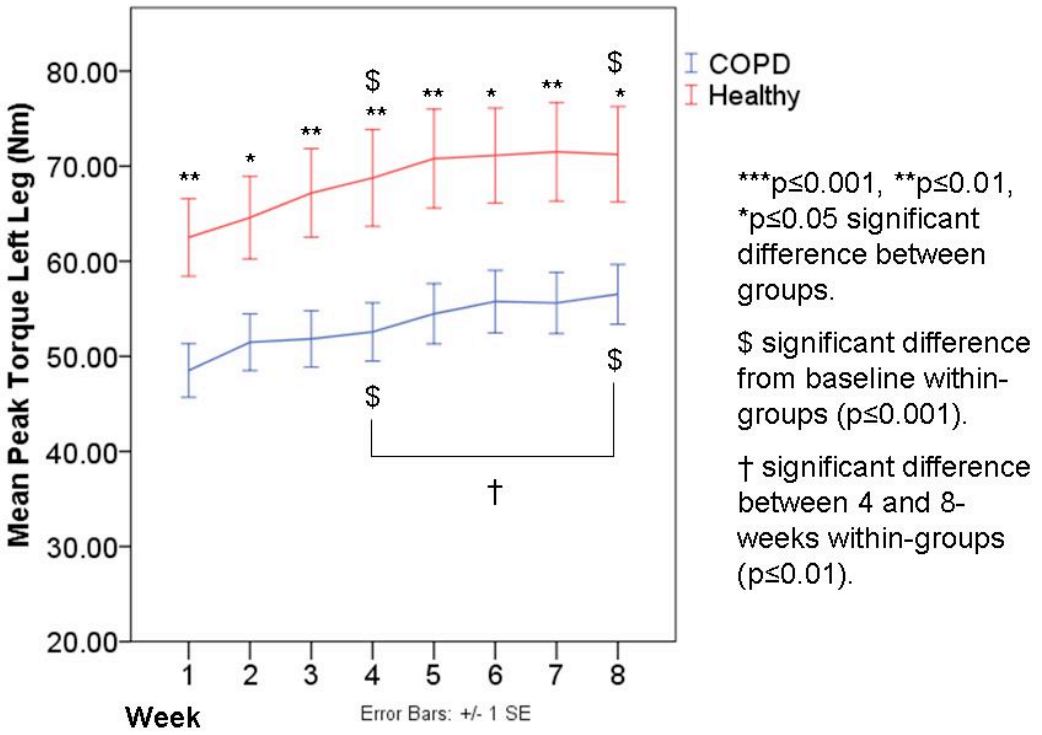


Figure 2. Training intensity progression of peak torque performed at weeks one to eight in patients with COPD and healthy controls

Table 1. Mean percentage change in isokinetic total work and peak torque for the left leg during the 8-week resistance training programme, in patients with COPD and healthy controls

Values are mean (SD)	**COPD Subjects**	**Healthy Controls**
Percentage change in work weeks 1-4	25.4 (28.6)	10.7 (14.9) *
Percentage change in work weeks 1-8	43.1 (50.3)	15.6 (17.2) *
Percentage change in torque weeks 1-4	9.3 (18.5)	7.8 (11.2)
Percentage change in torque weeks 1-8	19.8 (27.7)	13.5 (12.8)

*** p<0.05 between group difference**

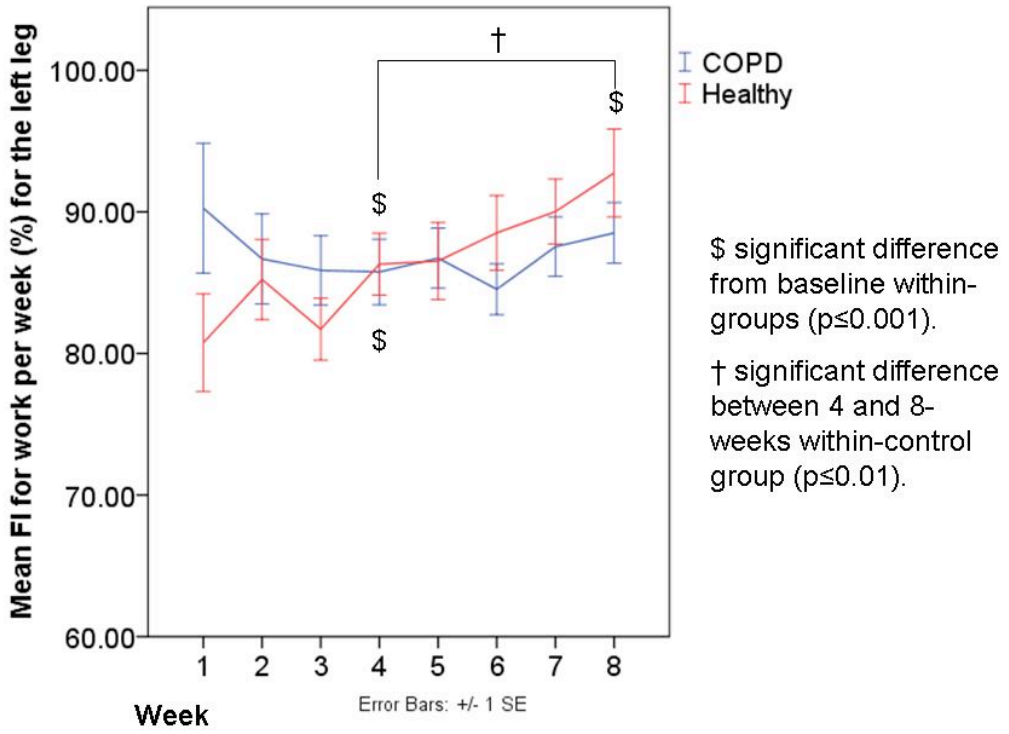


Figure 3. Mean fatigue index (FI) for work over 8-weeks in patients with COPD and healthy controls

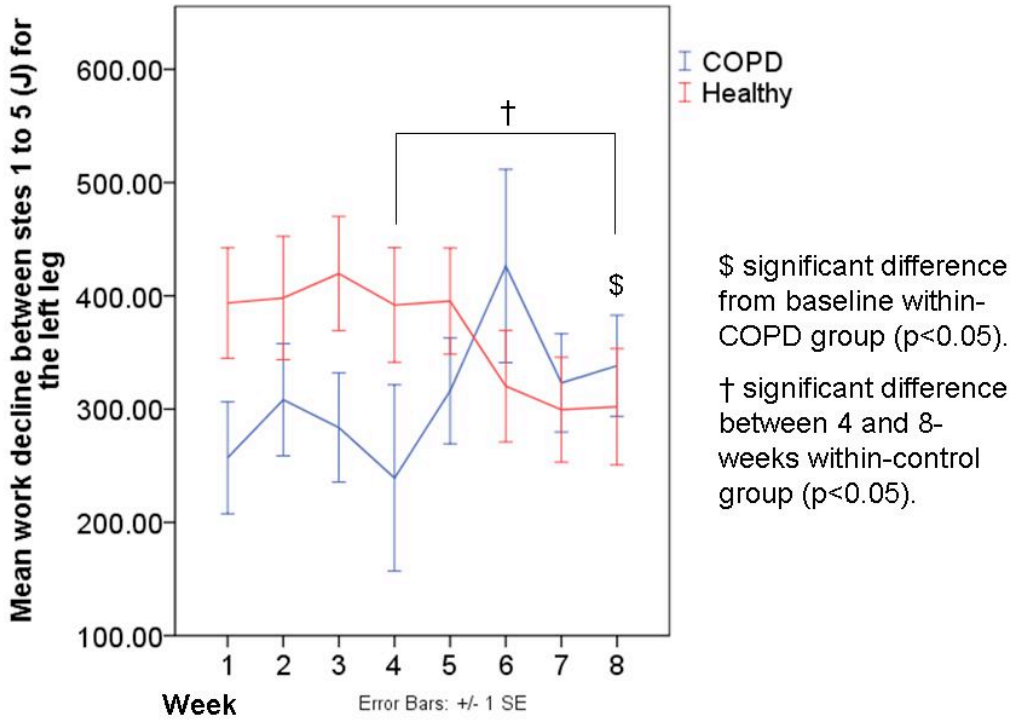


Figure 4. Absolute decline in isokinetic work between sets 1 to 5 averaged per week in patients with COPD and healthy controls

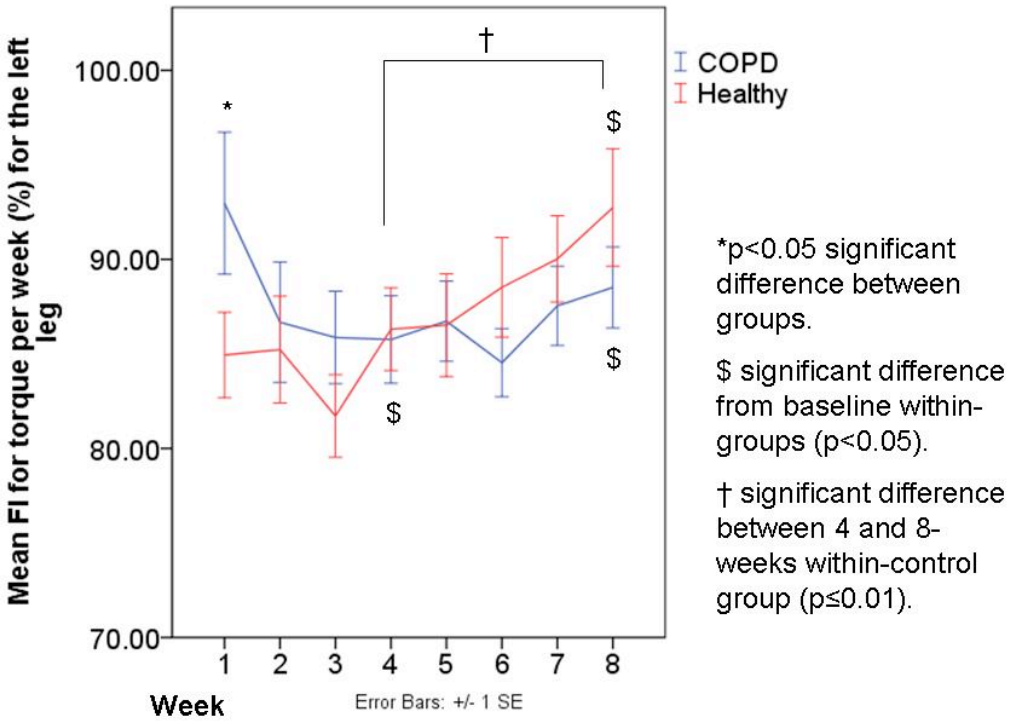


Figure 5. Mean fatigue index (FI) for torque over 8-weeks in patients with COPD and healthy controls

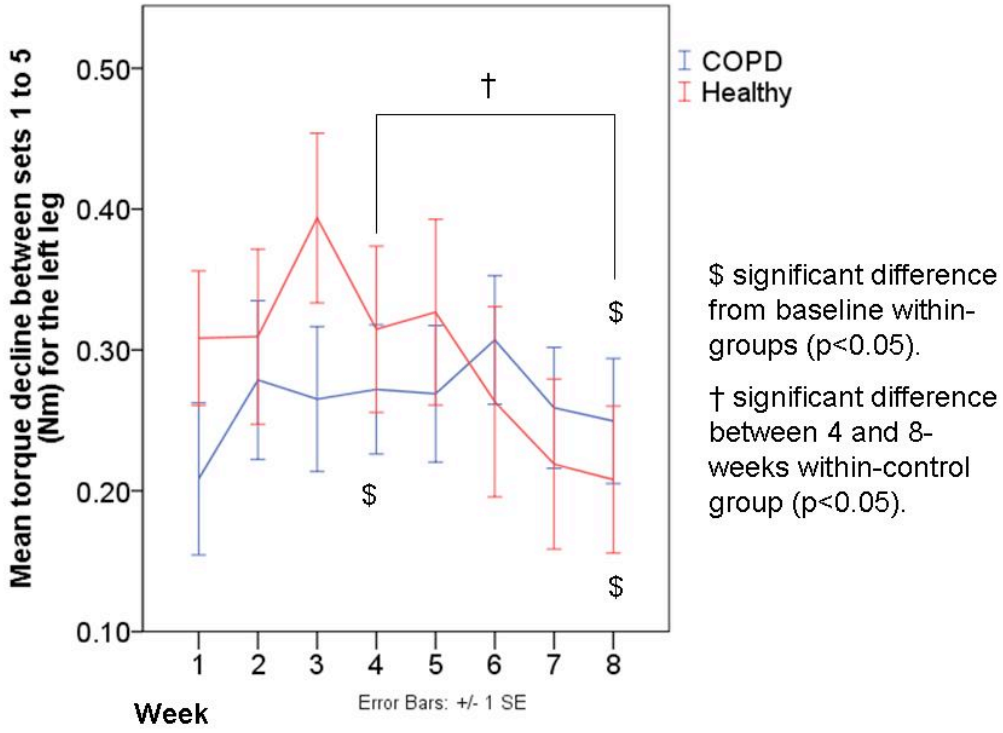


Figure 6. Absolute decline in isokinetic torque between sets 1 to 5 averaged per week in patients with COPD and healthy controls

Findings: The results for the left leg, presented in this appendix, broadly mirror the findings in chapter 5 (right leg). The training progression trajectories for total work (figure 1) and peak torque (figure 2) are a similar pattern to figures 5.1 and 5.2 (right leg, chapter 5). The absolute values are also similar. Again, healthy controls performed RT at significantly higher workloads and torque values compared to patients with COPD at all time points ($p \leq 0.05$) and this division between controls and COPD patients remained throughout. Both groups had significant within-group improvements in work and torque performed at four and 8-weeks compared to baseline. However there was a plateau in the healthy control group after 4-weeks (no significant improvement between weeks 4-8) for both outcomes. COPD subjects continued to have significant improvements in training workload and torque production between four and 8-weeks ($p \leq 0.01$).

The results in table 1 indicate that the majority of the progression in training work and torque for the left leg occurs within the first 4-weeks, for both groups. The percentage changes in isokinetic work exceeded changes in torque at both time points for patients with COPD. The magnitude of changes was generally the same as in table 5.1 (chapter 5, right leg). Although percentage improvements in the left leg for work performed exceed the changes in the right leg for patients with COPD (left leg weeks 1-8= 43.1%, right leg weeks 1-8= 25.4%). There was a statistically significant between-group difference for the percentage change in isokinetic work in weeks 1-4 (10.7% for controls, 25.4% for patients with COPD, $p<0.05$).and weeks 1-8 (15.6% for controls, 32.4% for patients with COPD, $p<0.05$).

Figures 3 and 4 display the FI and absolute decline for work produced in the left leg. There were no significant differences between the two groups, at any time point for FI and work decline. The FI remained at around 90% in patients with COPD but improved in control subjects over the 8-week period, suggesting improved FR in this group. The mean absolute workload decline each week was greater for the left leg (figure 4), when compared to the right leg (figure 5.4, chapter 5).

Figures 5 and 6 outline the FI and absolute decline for torque produced in the left leg. At week one patients with COPD had a significantly higher torque FI compared to healthy controls ($p<0.05$). Differences between groups were not apparent at any other time point for FI and for torque decline. Furthermore, torque declines each week were much lower for the left leg (figure 6) when compared to the right leg (figure 5.6, chapter 5).

Appendix 15

Wearing your Activity Monitor

We ask you to wear your activity monitor for 7 consecutive days during waking hours. This will measure the times that you are active throughout the day.

Please wear your monitor at the following times each day:

Day	Date	Time Monitor on	Time Monitor off
1			
2			
3			
4			
5			
6			
7			

- You do not need to switch the monitor on just attach it to your belt or belt hook when you get dressed in the morning. If you remember, press the 'mark' button each morning when you first put the monitor on.
- Take the monitor off each evening and again, if you remember, press the 'mark' button each evening when you take the monitor off.
- Aim to wear the monitor for approximately the same number of hours each day. For example, 9am to 9pm.
- The monitor is lightweight and shouldn't interfere with your everyday activity, just carry on with your daily routine as normal.
- Take off the monitor if you have a bath/shower or when washing. Try not to get the monitors wet.

Please return the monitor when you attend for your next visit or if this is your last visit, the monitor will be collected from your house on……. at ……..

Thank you for your commitment to this research study. If you have any problems or questions then please call: **Linzy Houchen- 0116 256 3652.**

Appendix 16

Duke Activity Status Index (DASI)

Please answer the questions below by circling the appropriate response **Yes or No.**

Can you:

		Weight	
1.	Take care of yourself, that is, eat, dress, bathe or use the toilet?	2.75	Yes/No
2.	Walk indoors, such as around your house?	1.75	Yes/No
3.	Walk a one mile or two on level ground?	2.75	Yes/No
4.	Climb a flight of stairs or walk up a hill?	5.50	Yes/No
5.	Run a short distance?	8.00	Yes/No
6.	Do light work around the house like dusting or washing dishes?	2.70	Yes/No
7.	Do moderate work around the house like vacuuming, sweeping floors or carrying groceries?	3.50	Yes/No
8.	Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	8.00	Yes/No
9.	Do garden work like raking leaves, weeding or pushing a power mower?	4.50	Yes/No
10.	Have sexual relations?	5.25	Yes/No
11.	Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis or throwing a cricket ball or football?	6.00	Yes/No
12.	Participate in strenuous sports like swimming, singles tennis, football?	7.50	Yes/No

$V0_2MAX = 0.43 \text{ X DASI} + 9.6$